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Update in Gastroenterology

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Developments in gastroenterology continue to be in the limelight in the new millennium. Advances in basic science, laboratory technique, endoscopic procedures and imaging modalities have fuelled innovations in the diagnosis and treatment of digestive diseases. In this issue of the Diary, several disease entities have been selected for review, either because of the interest in them among practitioners or the amount of knowledge accrued in recent years. A short description of each chosen topic is given below.

It is said that the only good Helicobacter pylori is a dead one. Every effort has been made to eradicate this bug in the setting of duodenal or gastric ulcer. Eradication of H. pylori can potentially reduce the risk of gastric cancer development, particularly before the appearance of pre-neoplastic changes like atrophy and intestinal metaplasia. While a one-week course of triple therapy has been the standard treatment locally, a longer course of 14 days is used in the US. Furthermore, a novel 10-day sequential therapy has shown to be effective in a number of studies. For rescue therapy, quadruple therapy and levofloxacin-amoxicillin-based triple therapy are useful options. After successful eradication, the average annual reinfection rate is low, probably around 1%.

Gastro-oesophageal reflux-induced disease (GERD) has become the most common gastrointestinal disorder in the West and its incidence is also rising in the Asia-Pacific region. Empiric therapeutic trial of proton pump inhibitors (PPI) has been the recommended initial treatment. Endoscopy is usually performed in patients refractory to treatment, having alarm signs or symptoms or in middle age. A number of GERD patients with persistent symptoms may be benefited by PPI b.d. Extra-oesophageal manifestations have been linked to GERD, including atypical chest pain, asthma/chronic cough, laryngeal symptoms and signs, and sleep disturbance. Barrett's oesophagus and oesophageal adenocarcinoma, as complications of GERD, are not common in Hong Kong. There are new advances in the pH and impedance studies of GERD, which increase the diagnostic accuracy. Endoscopic and surgical treatments are available for patients who refuse to take long-term medication.

Many clinicians have witnessed that the once uncommon inflammatory bowel diseases (Crohn's Disease (CD) and Ulcerative Colitis (UC)) are now increasingly encountered in local practice. The cause of this rise is not certain but may be associated with environmental changes due to urbanisation and adoption of the western style of living, culture and diet. Higher socioeconomic class may also be implicated in disease development. The CARD15/NOD2 single nucleotide polymorphisms (SNPs) are associated with CD in Caucasians but CARD15/NOD2 mutations in Chinese CD are virtually absent. Ulcerative proctitis has been reported to be the commonest type of disease in UC, while extensive colitis is a frequent finding too.

In developed countries, nonalcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease. NAFLD is now reaching an epidemic scale in Asia. In a study in China, around 15% of the adults were found to have NAFLD. The disease is certainly not

benign and can progress to liver cirrhosis, liver failure and hepatocellular carcinoma. NAFLD is closely associated with the metabolic syndrome and cardiovascular disease, and these conditions must be evaluated together. Liver biopsy has been the gold standard for disease assessment. Because of the limitations and risks of liver biopsy, non-invasive tests for liver fibrosis have been developed and they include serum biomarkers and elastography techniques (Fibroscan). Treatments of NAFLD include lifestyle management, dietary intervention, insulin sensitisers (metformin and thiazolidinediones), anti-oxidants and bariatric surgery.

An important function of the liver is the detoxification of exogenous compounds. The organ itself is, at the same time, exposed to the toxicity of these substances. Drug-induced liver injury (DILI) accounts for more than half of the cases of acute liver failure. The real incidence of DILI is not known because of the difficulty in making the diagnosis and the low frequency of reporting. The common hepatotoxic agents in clinical practice are paracetamol, amoxicillin/clavulanic acid, anti-tuberculosis drugs, thiazolidinediones, statins, etc. Another group of medications widely used in Hong Kong, which may cause liver injury, are herbal products.

Antiplatelet agents are two-edged swords. On the one hand, they effectively reduce the vascular complications of atherothrombotic diseases. On the other hand, they frequently cause adverse gastrointestinal events, ranging from mild dyspepsia to life-threatening bleeding or perforation from peptic ulcer. Aspirin and clopidogrel are the two commonly used antiplatelet agents. The clinical efficacy of clopidogrel in the secondary prevention of vascular complications is marginally better than aspirin. In contrast, the incidence of severe adverse upper gastrointestinal (GI) events is significantly lower for clopidogrel compared with aspirin. Clopidogrel appears to be safer than aspirin in patients with no history of peptic ulcer disease or GI bleeding. In patients with dyspeptic or moderately severe bleeding peptic ulcers, conversion to clopidogrel or continuation of aspirin is safe if the patients are simultaneously maintained on proton pump inhibitors.

I hope this brief introduction can arouse readers' interest in the following review articles by the experts in different areas, whose help I have the honour to enlist.

The Editor's Message

On behalf of the Editorial Board of the Hong Kong Medical Diary, I would like to inform our readers that the editor-in-chief, Dr. Walter King, has recently decided to resign from the post and I will take up his work from now on. The Editorial Board wishes to express the gratitude to Dr. Walter King for his enormous contribution in the past few years during which he has transformed the diary into a widely circulated local medical publication and a forum for the dissemination of medical information and knowledge in various medical and dental specialties in Hong Kong. To keep up with his good work, I have to call upon all editors in the Editorial Board, all issue editors and all member societies to continue contributing comprehensive evidence-based articles of the highest quality. With the wide circulation to the 9,000 medical doctors and dentists in its distribution list and the internet version on the web page of the Federation of Medical Societies of Hong Kong, I certainly hope that both our medical and dental colleagues as well as the general public can easily find the relevant medical information and services in Hong Kong when needed.

Dr. Mok Chun On
Editor-in-chief
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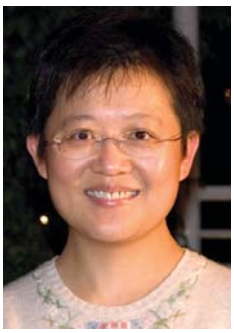
Helicobacter pylori - The Legendary Bug



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Helicobacter pylori is a helical shaped, microaerophilic, flagellated Gram-negative bacterium. Its discovery dated back to 1875 but it could not be grown in culture at that time.[1] In 1979, the bacterium was rediscovered by Dr. Robin Warren. Dr. Barry Marshall joined the research in 1981. They published the association of the bacteria and gastritis in 1983.[2] In recognition of their discovery, Drs. Warren and Marshall became Nobel Laureates in 2005.

Epidemiology

Nearly half of the world population is infected with *H. pylori*.[3] Its prevalence correlates inversely with the socio-economic status of a country.[4] Using a commercial enzyme-linked immunosorbent assay kit for anti-HP IgG antibody on 397 volunteers who attended medical health exhibitions in October 1993 and May 1994, prevalence of H. pylori infection was found to be 58.4% in Hong Kong.[5] More than 90% of duodenal ulcer patients were infected.[6] *H. pylori* positive patients develop duodenal ulcer at a rate of ~ 1% per annum. A lower prevalence of *H. pylori* is observed in patients with gastric ulcer, a higher proportion of which is related to the use of aspirin and non-steroidal anti-inflammatory drugs.

The bacteria have been isolated from faeces,[7] saliva[8] and dental plagues[9] of infected patients. The routes of transmission are suggested to be gastro-oral and faecal-oral. An epidemiological study performed in Melbourne Chinese immigrants showed the use of chopsticks as a risk factor for *H. pylori* infection, irrespective of their socio-economic status.[10] Leung et al.[11] tested the hypothesis of transmission via the use of chopsticks by attempting to culture the bacteria from saliva and chopsticks of 45 infected volunteers. All cultures were negative. *H. pylori* was detected by PCR in the saliva from 15 (33%) infected subjects and on the chopsticks from one (2%). Twelve sets of pooled chopsticks, ten in each set, were collected from the cafeteria. Washings were obtained for PCR. *H. pylori* was tested positive in only two sets. This demonstrated a low risk of contracting the infection through the use of chopsticks.

Diagnosis

Various diagnostic tests are available in the market. Basically they can be divided into invasive and non-invasive tests.[12] Invasive tests include biopsy-based rapid urease test, histology, culture and molecular tests. Non-invasive tests can further be classified into passive and active tests. Passive tests include serological testing of IgG in serum, IgA in saliva, and IgG in urine. There is a trend towards development of the office-based serology tests for rapid diagnosis. A Canadian study[13] performed for dyspeptic patients in the primary care setting, however, found a high false positive rate of 33%. It is still early to recommend the use of near-patient tests for making a diagnosis of *H. pylori* infection. Active tests serve to detect the presence of *H. pylori* and hence they provide evidence of a current infection. Currently available active tests include the urea breath test and stool antigen test.

Before a test can be employed in the community, local validation of its accuracy is required. Tests can be done by a technician but their interpretations require medical knowledge. The accuracy of biopsy-based rapid urease test is decreased in the setting of acute ulcer bleeding due to the buffering effect of serum albumin.[14] Albumin, by releasing hydrogen ions, buffers the alkaline effect of ammonia and suppresses the colour change of the pH indicator. It was found that *H. pylori* was detected in 93% of nonbleeding duodenal ulcers as compared with 71% of bleeding duodenal ulcers by the biopsy urease test.[15] There were cases where the bacteria, failed to be detected by biopsy urease test, were identified by histology.

Achlorhydria causes false-negative urease test results (biopsy and breath tests). Without the neutralising effect of acid, *H. pylori* is killed by the action of its own urease.[16] Proton pump inhibitor (PPI), antibiotics and bismuth-containing compounds can reduce the density and / or urease activity of *H. pylori*.[17] When given a standard dose of PPI for treating gastro-oesophageal reflux disease, 33% of the *H. pylori*-infected patients were tested negative by the urea breath test. Their tests returned positive 14 days after stopping the drug.[18] Serial changes of urea breath test results in hospitalised patients taking antibiotics for chest or urinary tract infection were studied.[19] One third of *H. pylori*-infected individuals had transient false-negative results. It occurred within 24 hours of antibiotics treatment and reverted back to normal at six-week post treatment.

It has been recommended to withhold bismuth and antibiotics for at least 28 days and PPI for 14 days prior to *H. pylori* testing by the urea breath test.[17] It is controversial whether H2-receptor antagonists affect test sensitivity but most laboratories would suggest to

withhold it for 48 hours before testing.[17] Despite the high sensitivity of histology, the site, numbers and size of the biopsies can have great impact on diagnostic accuracy. A single biopsy taken in the lesser curvature, close to the incisura, can detect the presence of *H. pylori* in 90% of the cases.[12] Accuracy can be improved by taking additional biopsies from the greater curvature of the antrum and the greater curvature of the corpus. The American College of Gastroenterology has recommended a minimum of three biopsies to be taken for diagnosis.[17]

Treatment

The backbone of eradication therapy remains unchanged in all these years. Standard first line treatment comprises of a PPI and two antibiotics. A one-week course of this triple therapy was endorsed by The Asia-Pacific Consensus Conference[20] in 1997 and The Maastricht III Consensus Report[21] in 2007. In the United States, the same therapy is recommended to be given for 10 to 14 days.17 The efficacy of triple therapy has been decreasing to about 80%.[22] The drop in effectiveness is related to a rising trend of antibiotic resistance. Choice of antibiotics should be determined by the level of resistance in the locality. The European Helicobacter Study Group recommended that clarithromycin should not be used if the resistance rate reaches 15-20%.[21] In vitro metronidazole resistance is less of a concern since it does not reflect in vivo resistance. The prevalences of resistance to clarithromycin, amoxicillin and metronidazole in Hong Kong were 7.8, 0 and 39.2% in a recent report.[23] Bismuth-containing quadruple therapy has been suggested as an option for first line treatment in view of the increased resistance to both clarithromycin and metronidazole.[21] Besides antimicrobial resistance, patients' compliance plays a role in determining the success of treatment. Eradication rate dropped from 96% to 69% in patients who took less than 60% of their prescribed medication.[24] Although it is common to experience taste disturbance with clarithromycin and metronidazole and diarrhoea with amoxicillin, they are usually mild. Patients should be assured on the short-term nature of the side effects and encouraged to complete the course.

Sequential Therapy

A novel 10-day sequential therapy was shown to be effective in a number of studies carried out in Italy. [25-28] It consists of 5-day dual therapy with a PPI plus amoxicillin, followed by 5-day triple therapy with a PPI, clarithromycin and tinidazole. Amoxicillin has dual actions. First it helps to lower the bacterial load so as to improve the efficacy of the immediately subsequent short course of triple therapy.[29] Secondly, it is speculated that, after weakening the cell wall of the bacterium, amoxicillin prevents the development of efflux channels through which clarithromycin is transferred out of the bacterium.[28] In a pooled-data analysis[29] of two pilot studies and 13 randomised trials on over 1800 patients, sequential therapy achieved *H. pylori* eradication rate of 93.5% at intention to treat analysis. It was found to be promising in treating antibiotics resistant organisms. Infection was cured in 16/48 patients (33.3%) infected with clarithromycin (with or without metronidazole) resistant strains, and 68/72 patients (95.8%) infected with metronidazole resistant strains. Compliance and side-effect profile were comparable to standard triple therapy. No difference in eradication rate was observed among different PPIs, and between patients suffering from peptic ulcer or non-ulcer dyspepsia. This new regimen, however, is not suitable for patients with penicillin allergy and its effectiveness has to be verified by centres in other parts of the world.[22]

Rescue Therapy

The principle for choosing a rescue therapy is to avoid using antibiotics which have been used in first line treatment.[17] Quadruple therapy, if not given as the first line treatment, is a preferred option.[21] Recently levofloxacin-amoxicillin-based triple therapy was found to be superior to quadruple therapy in two meta-analyses.[30, 31] It was found to be better tolerated with a lower incidence of side effects prompting discontinuation of therapy.[31] Ten-day regimens, giving an eradication rate of over 80%, were more effective than 7-day combinations,[30, 31] while no difference was observed with 500mg daily versus 250mg bd dosing of levofloxacin.[31] Emergence of levofloxacin resistance strains, however, may limit its application. It is still unknown whether the resistance is absolute, as in the case of clarithromycin, or more relative as with metronidazole.[17] The ten-day therapy was found to be effective in a pilot study on 35 patients who had failed the sequential regimen. The eradication rate was 85.7% at intention-to-treat analysis.[32] Rifabutin-based triple therapies were tested by several groups and found to be useful as salvage therapy.[33-36] The presence of clarithromycin or metronidazole resistance did not affect efficacy of treatment.[36] It is, however, limited by the potential adverse reactions characterised by fever and myelotoxicity. Large-scale use of this drug is not advisable for the fear of selecting resistance among Mycobacteria.[21]

Gastric cancer

The incidence of gastric cancer in Hong Kong is 15.6 per 100,000.[37] Over 1000 new cases were diagnosed in 2005. The average mortality rate was 9.3 per 100,000. *H. pylori* was classified as a grade 1 carcinogen by the International Agency for Research on Cancer in 1994.[38] The infection is associated with approximately two-fold increased risk of developing gastric cancer,[39] equally strong for both the intestinal and the diffuse type.[40] This association is only observed for cancers developed in the non-cardiac region.[41] CagA positivity further increased the risk of cancer by 2.01 fold. Searching for CagA status over *H. pylori* infection may confer additional benefits in identifying populations at greater risk for gastric cancer.[41] But this association may not be true in the Asian population.[42] In a prospective follow-up of more than 1500 Japanese patients suffering either from upper GI pathology (peptic ulcers or gastric hyperplasia) or nonulcer dyspepsia, gastric cancers developed in 2.9% of the infected patients after a mean of 7.8 years, but not in the uninfected individuals.[43] Histology findings of corpus-predominant gastritis, severe gastric atrophy, and intestinal metaplasia put patients at an increased risk. These histological findings

were proposed as precancerous cascade in the development of gastric cancer.[44] Apart from the infection, host genetic and environmental factors also contribute to the risk.[21]

It remains unknown whether *H. pylori* eradication would reduce the risk of gastric cancer.[45] It is unlikely that by simply removing the organism will translate into a perceptible reduction in gastric cancer risk within a short time frame.[46] There are a number of human intervention studies looking into the effect of *H. pylori* eradication in the progression of precancerous lesions. It leads to the concept of 'point of no return'.

The Chinese University of Hong Kong and the Beijing Medical University conducted a collaborative study in the county of Yantai, Shangdong Province, China, where there is a high incidence (50 per 100,000) of gastric cancer.[42] Endoscopic surveys were conducted. 587 *H. pylori* infected volunteers were randomised to triple therapy or placebo. Both acute and chronic gastritis decreased in both the gastric antrum and corpus and activity of intestinal metaplasia also decreased in the antrum one year after *H. pylori* eradication. There was, however, no regression of intestinal metaplasia or gastric atrophy. Within 5 years after *H. pylor*i eradication, remarkable reduction in severity and activity of chronic gastritis and marked resolution of intestinal metaplasia in the antrum were observed.[48] Continuous *H. pylori* infection leads to progressive aggravation of atrophy and intestinal metaplasia. In their separate report, duodenal ulcer was found to be an independent protective factor, while persistent *H. pylori* infection, alcohol use and drinking water from a well were independent risk factors associated with intestinal metaplasia progression.[49] They concluded that eradication of *H. pylori* is protective against progression of premalignant gastric lesions. A randomised, controlled chemoprevention trial conducted in Columbia showed that by curing *H. pylori* infection, a modest regression of intestinal metaplasia compared with placebo (15% vs 6%) was observed at 72 months.[50] In their multivariate analysis at 12 years of follow-up on 795 patients, the preneoplastic lesions were found to regress at a rate equal to the square of time patients having free from the infection.[51]

A randomised controlled trial was conducted in Changle County, Fujian Province, Southern China, to determine whether treatment of *H. pylori* infection reduced the incidence of gastric cancer.[52] 1630 healthy *H. pylori* carriers were randomised for two-week triple therapy or placebo. They were followed up for an average of 7.5 years. 18 new cases of gastric cancers were reported. In the subgroup of infected volunteers without precancerous lesions (gastric atrophy, intestinal metaplasia and dysplasia) at presentation, six patients in the placebo group whereas none in the treated group developed gastric cancer. In the remaining twelve patients in which precancerous lesions were present at presentation, seven were from the treatment and five were from the placebo group. It puts forward the concept of 'point of no return' at which *H. pylori* should be eradicated before reaching the state of intestinal metaplasia in the cascade of cancer development. Eradication of *H. pylori* has the potential to reduce the risk of gastric cancer development, optimally before the development of pre-neoplastic lesions like atrophy and intestinal metaplasia.[21]

Reinfection

After successful *H. pylori* eradication, how often would we get re-infected? Re-infection should be distinguished from recrudescence which usually occurs early after treatment. It means reappearance of the original strain of *H. pylori* following its temporary suppression. One would expect high reinfection rates in countries with high prevalences of *H. pylori* infection. Reinfection rate was determined in 184 Chinese patients with duodenal ulcer disease who had been shown to have their *H. pylori* eradicated.[53] It was conducted in Guangzhou, with a high age-standardised prevalence of ~56%. Over a period of 24 months, four patients were tested positive for *H. pylori* (three within six months and one at 24 months). DNA fingerprinting of isolates in one patient diagnosed *H. pylori* positivity at 6 month was found to have a strain identical to the pretreatment one. The average annual reinfection rate was found to be 1.08%. Similarly low rates of re-infection were found in other Asian countries.[54, 55] If identical strains were considered as recrudescence, the reinfection rate was found to be < 0.8% per patient year in a Japanese study over a period of two years.[56]

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Power to Protect From NSAID-associated Upper GI Side Effects[1-3]

Presentation: Esomeprazole film-coated tablet. **Indications & Dosage: Treatment of erosive reflux esophagitis** 40mg once daily for 4 weeks. **Long-term management of patients with healed esophagitis to prevent relapse** 20mg once daily. **Symptomatic treatment of GERD** 20mg once daily. **In combination with an appropriate antibacterial therapeutic regimen for the eradication of Helicobacter pylori:** *Healing of H. pylori associated duodenal ulcer OR as prevention of relapse of peptic ulcers in patients with H. pylori associated ulcers:* 20mg esomeprazole with 1g amoxicillin & 500mg clarithromycin, all bd for 7 days. **Patient requires continued NSAID therapy** *Healing of gastric ulcers associated with NSAID therapy:* 20mg once daily for 4-8 weeks. *Prevention of gastric & duodenal ulcers associated with NSAID therapy in patients at risk* 20mg once daily. **Contraindications:** Hypersensitivity to esomeprazole; substituted benzimidazoles; hereditary fructose intolerance; glucose-galactose malabsorption or sucrase-isomaltase insufficiency. **Precautions:** Maximum dose for severe liver impairment is 20mg; Long-term treatment; Pregnancy & lactation. **Interactions:** Ketoconazole; itraconazole; drugs metabolized by CYP2C19 (eg diazepam, citalopram, imipramine, clomipramine, phenytoin); warfarin; cisapride; clarithromycin. **Undesirable effects:** Headache, abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation. **Full local prescribing information is available upon request. API.HK.NEX.1104**

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A Guiding Star in Gastroenterology

HK.NEX.0108.02 02/2008

On Gastro-oesophageal Reflux-Induced Diseases

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Dr. Ambrose CP Kwan

This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded one CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 March 2008.

Gastro-oesophageal reflux-induced diseases (GERD) are commonly encountered gastro-intestinal disorders and classical symptoms include heartburn, acid regurgitation and atypical chest pain. Oesophageal manifestations and complications of GERD include erosive oesophagitis, oesophageal stricture, Barrett's oesophagus and oesophageal adenocarcinoma. The wide range of extra-oesophageal associations includes sleep disturbance, cough, laryngitis, laryngeal cancer, hoarseness, asthma, sinusitis and dental erosion. There is a perception that the prevalence of GERD is increasing in Asia and the prevalence assessed at two time-points in one city was rising in China and Singapore[1]. Obesity, hiatus hernia, smoking and psychosocial factors like heavy workload, anxiety, divorce have been shown to be associated with GERD or heartburn[2]. Although the prevalence of Barrett's oesophagus and adenocarcinoma of oesophagus is still low in HK Chinese, unexpectedly high figures were reported in Xi'an[3] and Japan[4].

1. Pathophysiology of GERD

The contribution of hiatus hernia to GERD is well known. The hiatus hernia eliminates the contribution of the crural diaphragm to lower oesophageal sphincter function and thereby promotes gastro-oesophageal reflux, especially when intragastric pressure is increased due to distension or straining of the abdominal musculature. The most common cause of GERD in the West is an excessive exposure of the oesophagus to acid and pepsin during transient lower oesophageal sphincter relaxation (TLESR). These periods last for 10-30 seconds in normal persons to help to vent gas from the stomach but they are frequently associated with acid reflux in GERD patients. Once gastric acid is in the oesophagus , clearance mechanisms are activated to rapidly propel the acid back to the stomach and in patients with impaired oesophageal motility, they are more prone to develop GERD. Gastric factors also play a role. Abnormal postprandial distribution of meal in the stomach and delayed gastric emptying are associated with reflux. A recent study from HK[5] reported that impaired oesophageal acid clearance was the major mechanism of GERD.

2. Clinical approach to patients with classical GERD symptoms

Empiric trial of proton pump inhibitors (PPI) or a high dose PPI b.d. as a diagnostic test is widely recommended as the initial treatment. In a study of Chinese patients with GERD symptoms[6] using high dose PPI for 2 weeks and a 50% reduction of symptoms as a positive response, the sensitivity and specificity of the high dose PPI test were reported to be 84% and 71% respectively, based on endoscopy or 24 hour pH study as gold standard. Endoscopy is usually reserved for refractory patients or those with alarm signs or symptoms such as anaemia, weight loss or dysphagia. An Asia consensus group[7] recommended endoscopy for patients older than 35 years of age. Endoscopy allows identification of other benign or malignant diseases (e.g. oesophageal candidiasis), diagnosis of Barrett's oesophagus and classification of patients into those with mucosal disease (reflux oesophagitis) and those without (NERD). Those with mucosal disease required high dose PPI for at least 8 weeks as a recent study on low dose PPI for 8 weeks only led to complete mucosal healing in 48% of patients[8]. Patients with NERD can be managed with step down or step up approach with PPI on a p.r.n. basis. Dietary advice and weight reduction may help some patients. Fortunately most patients with GERD in HK belong to mild erosive disease or NERD but stricture is occasionally encountered (Figure 1).

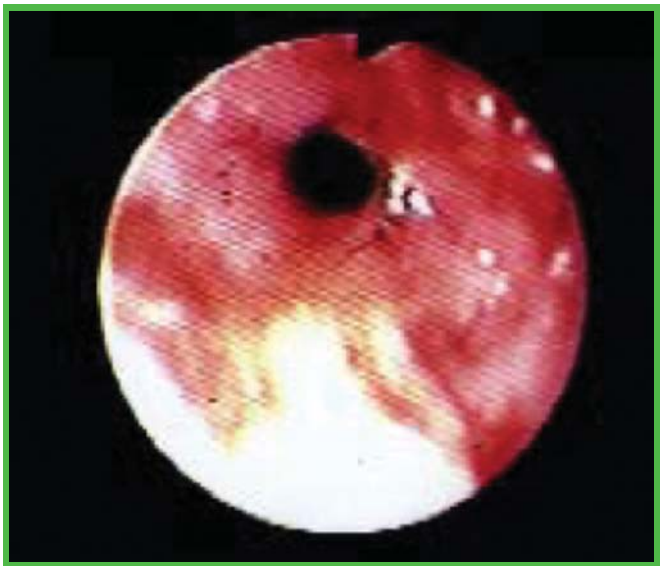

Figure 1. A 38 year old Chinese lady with long history of SLE complained of acid regurgitation and dysphagia. Endoscopy with pediatric endoscope showed a stricture at the oesophago-gastric junction. The stricture responded to a course of PPI therapy.

3. Extra-oesophageal manifestations of GERD

Convincing evidence exists linking each extra-oesophageal manifestation to reflux in some patients. However a causal relationship remains difficult to establish. The three most commonly investigated conditions are atypical chest pain, asthma and otolaryngeal manifestations. Data substantiating a significant beneficial effect of reflux treatment on symptoms are weak. Symptom relief may be incomplete for several reasons. First, these patients have heightened sensitivity to many different stimuli in the oesophagus. Consequently small amounts of acid could trigger these symptoms. Complete symptom control may be accomplished only by elimination of reflux which is rarely possible with even the best medical or surgical therapy. Secondly, these extra-oesophageal syndromes are usually multi-factorial with GERD as one of the several potential aggravating cofactors.

3a. Atypical chest pain

Individuals with acid reflux may also experience atypical chest pain, i.e. chest pain in patients for whom the results from cardiac work up were negative. It is believed to be one of the most common extra-oesophageal manifestations of acid reflux disease. In a local study[9] based on telephone interview, 50% of patients with atypical chest pain had symptoms of GERD. A simple approach is to give high dose PPI for 1-2 weeks and a 50% reduction of symptoms is regarded as positive response. Endoscopy or 24 hour pH study or manometry are reserved for refractory cases.

3b. Asthma and chronic cough

Surveys suggested that 30-90% of asthmatic adults had reflux symptoms or abnormal oesophageal acid exposure and many studies showed an association between these two conditions. The value of identifying reflux in individual patients with asthma is now becoming more widely recognised. The recognition of reflux in asthma patients is important because some bronchodilators, which are often used to treat asthma symptoms, may themselves exacerbate reflux by contributing to relaxation of the lower oesophageal sphincter. Such commonplace asthma therapy may therefore indirectly exacerbate respiratory symptoms in some patients with asthma.Several mechanisms might link reflux with asthma. As well as reflux bronchoconstriction caused by the aspiration of refluxed stomach contents into the bronchi, small amount of acid regurgitation in the oesophagus may cause increased bronchial reactivity via a vagally transmitted reflex. The clinical benefits of PPI therapy on asthma patients in randomised trials are however not as great as expected. There is a significant benefit in improving symptoms and reducing asthma medications usage but no objective improvement in pulmonary function test. Those patients with nocturnal respiratory symptoms and GERD symptoms seem to respond best. A subset of patients responded dramatically to anti-reflux surgery with complete asthma resolution[10] but the criteria for selection of patients for surgery is still unclear.

Gastro-oesophageal reflux may also be responsible for some cases of chronic cough but complete treatment response to medical treatment is rare in randomised controlled trials. The only strong support for the link comes from surgical studies that reported a significant resolution of symptoms in a subgroup of patients[11] after laparoscopic fundoplication. Again, the criteria for selection of patients for surgery is not yet clear.

3c. Laryngeal signs and symptoms associated with gastro-oesophageal Reflux

Four to ten per cent of patients in the West presenting to otolaryngologists have reflux symptoms, and reflux is associated with hoarseness, chronic laryngitis, vocal cord ulceration and even carcinoma of the larynx. In a local study of 28 patients with throat symptoms like globus, throat discomfort, burping or cough lasting more than 1 month together with signs of laryngitis, 14% of patients showed objective evidence of acid reflux by pH monitoring[12]. In another local study[13] on 26 patients with globus, objective evidence of GERD was found in 30.8%. Similar to chronic cough, anti-reflux treatment only provides partial improvement in symptomatology and in some cases laryngoscopic appearance. There are probably many other co-factors in the aetiology of chronic laryngitis. Since pH study is not widely available, long term anti-reflux medication should only be continued for patients with both symptoms of GERD and/or signs of chronic laryngitis.

3d. Sleep disturbance

Insomnia, interrupted or poor quality sleep, is a common complication of gastro- oesophageal reflux. Recent data suggested that 50-80% of reflux patients might have disturbed sleep[14]. Some cases appear to be associated with a nocturnal breathing disorder such as snoring or obstructive sleep apnoea. Many others are probably simply due to full or partial awakening in response to reflux-induced thoracic discomfort such as regurgitation or heartburn.

4. Management of refractory GERD patient

After a 4-8 week course of morning dose of PPI, 25-42% of patients may still have reflux symptoms. At this point, the physician should ensure the patient's drug compliance and review the timing of the PPI dose (taken 30-60 minutes before meal). Endoscopy should be considered if not yet done. Some patients have predominantly nocturnal symptoms and one option includes changing the timing of the once daily dose from o.m. to before dinner. This would be based on intragastric pH data showing that overnight intragastric pH control is greater when once daily PPI is given before the evening meal, compared to the morning dose. Increasing the patient's proton pump inhibitors to b.d. is another obvious and straightforward choice but the cost of drug will be high. Another choice would be to use an H2 blocker at bed time but tachyphylaxis occurred rapidly. Performing a 24 hour pH study may help to analyse the relationship between pH and symptoms. The result of 24 hr pH study of a patient with atypical chest pain who failed to respond to once daily PPI is shown in Figure 2. The overall 24 hr acid output is within normal limits in this patient but there is a good correlation between chest pain and acid reflux. The result suggests acid sensitive oesophagus and the patient responds to a higher dose of PPI given twice daily.

For patients who have refractory oesophagitis despite a b.d. dose of PPI, there are however several differential diagnosis such as drug-induced oesophagitis, skin disease associated oesophagitis, hypersecretory state

such as Zollinger-Ellison syndrome, genotypic differences and eosinophilic oesophagitis (diagnosed by biopsy). Endoscopy appearance of drug associated oesophagitis may range from one or more discrete ulcers to diffuse inflammation with exudates, or even stricture and pseudo-tumour formation. The most common site is the junction of the proximal and middle third of the oesophagus where peristalsis is weaker and where the aorta crosses the oesophagus. Common drugs include doxycycline and tetracycline, alendronate, aspirin and NSAID, potassium chloride, ascorbic acid, quinidine and ferrous sulphate. A variety of skin diseases may also cause oesophagitis such as lichen planus, pemphigus and pemphigoid. About 12-20% of Asians are said to be fast metabolisers of PPI. To date, all studies have been done with once daily dose of PPI and it is unknown if twice daily dosing may overcome the problem.

5. Barrett's oesophagus and oesophageal adenocarcinoma

In some patients with abnormal gastro-oesophageal reflux, the oesophageal mucosa responds with the development of metaplastic columnar-specialised intestinal epithelium (Barrett's oesophagus see Figure 3) an assumed risk factor for the development of oesophageal adenocarcinoma. In a recent American Society of Gastrointestinal Endoscopy guidelines[15], some of the recommendations for Barrett's oesophagus are as follows:

A. Screening gastroscopy for Barrett's oesophagus should be considered in selected patients with chronic long standing GERD. After a negative screening examination, further screening is not indicated.

B. For patients with established Barrett's oesophagus, biopsy should be taken to look out for dysplasia. After 2 consecutive negative examinations for dysplasia in 1 year, further examination after 3 years is acceptable.

C. For patients with low grade dysplasia, further surveillance is recommended although the interval of surveillance is controversial.

D. For patients with high grade dysplasia, there is a significant risk for cancer and management options including frequent repeat endoscopy, oesophagectomy, endoscopic photodynamic therapy, endoscopic mucosal resection(EMR) should be discussed with patients.

In U.S, the pillcam (capsule endoscopy for the oesophagus) has been licensed to detect Barrett's oesophagus without the need of invasive endoscopy but it's not yet available in HK. Many new modalities like narrow band imaging (available in many hospitals already), magnifying endoscopy, chromoendoscopy and endo-microscopy have been developed to help to locate areas of suspicion of high grade dysplasia for biopsy and endoscopic treatment like mucosal resection or photodynamic therapy are options with variable success rate. Fortunately, the incidence of oesophageal adenocarcinoma is still low in HK but a rising trend is observed in Xi'an and Japan.

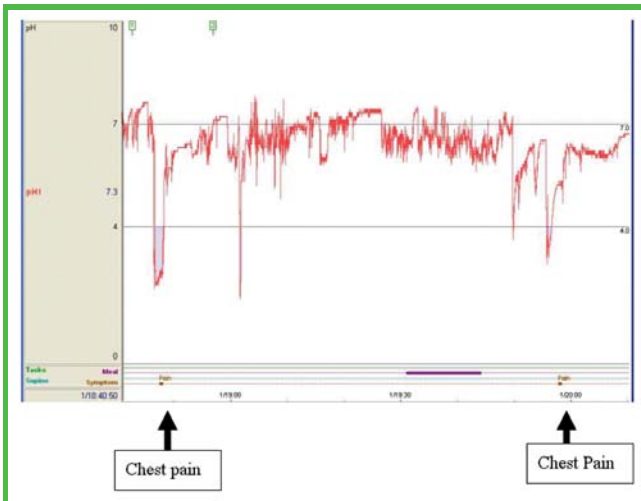

Figure 2. This was the result of 24 hour pH study of a 35 year old gentleman who complained of chest discomfort. His symptoms did not respond to once daily PPI therapy. The 24 hour acid reflux was within normal limits but there was a good correlation between acid reflux below 4 and 2 episodes of chest pain. He responded to twice daily dose of PPI.

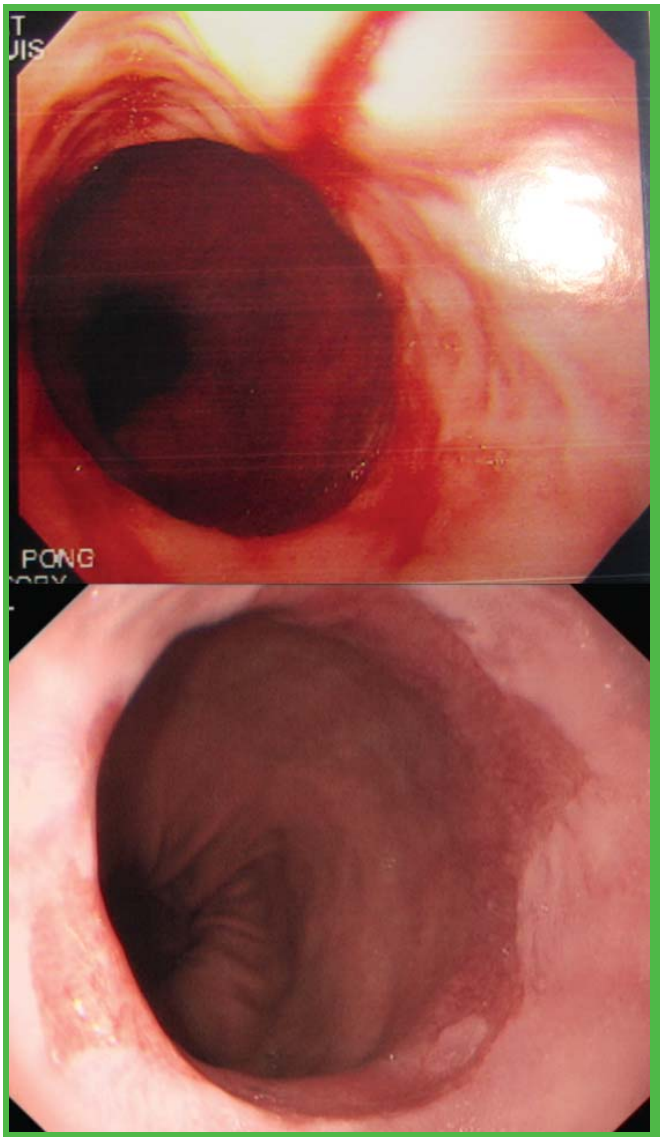

Figure 3. A 35 year old Caucasian patient complained of infrequent mild acid regurgitation and heartburn. Endoscopy showed reflux oesophagitis and hiatus hernia in the upper photo and 3 months after PPI therapy, oesophagitis resolved and biopsy confirmed Barrett's oesophagus without dysplasia in the lower photo.

6. New advances in pH and impedance study

More recently wireless bravo chip is available that can be affixed to the lower oesophagus. 48-72 hour pH data can be recorded via a portable data loggers and analysed by computerised devices. The bravo system has been shown to improve patients' compliance as compared to conventional pH study and allows greater patient freedom to continue normal daily activities. Extended 48 hour pH study is useful as around 25% of cases may have excessive acid reflux in a single day only. However, early detachment within 16 hours resulting in shorter period of recording and technical failure (e.g. batteries) are not infrequently reported. Chest discomfort has also been reported after bravo capsule attachment, possibly due to stimulated oesophageal contraction and occasionally requires removal of the chip. The device is also not widely available. The new multi-channel intraluminal impedance (MII) and pH study catheter can measure both acidic and non-acidic reflux at the same time and research is on-going to study its impact on clinical management.

7. Long term complication of PPI

Recently a retrospective data analysis[16] showed that long term PPI was associated with hip fracture. People over 50 years of age who took the drug for more than one year had a 44% increased risk of hip fracture. Taking PPI at higher dose and for longer periods pushed up the risk of hip fracture to 245%. The authors speculate that PPI stops gastric acid which is required for calcium absorption and they urge doctors to use the lowest effective dose of the drug. Other associations like C*lostridium difficile* associated diarrhoea and pneumonia have also been reported but the relationship remains speculative.

8. Endoscopic and surgical treatments for GERD

The Stretta procedure is an endoluminal radio-frequency energy delivery system for the treatment of GERD and obtained FDA approval in US since 2000. In a study up to 4 years[17], 75% of patients treated with Stretta procedure required no or fewer medications than before at the end of assessment. There is also a favourable impact on lower oesophageal sphincter pressure, oesophageal acid reflux and symptom scores as well. Over four thousand procedures had been performed and unfortunately, a few perforations and two deaths were reported in the early post-marketing phase. Preliminary experience in Japan[18] is promising and bigger studies in Asia are awaited. Other procedure like NDO plicator which can create a full thickness serosa-to-serosa apposition of the proximal cardia has also been approved in US but experience in Asia is limited.

Laparoscopic fundoplication has evolved as the surgical procedure of choice for patients with GERD. Although the durability of surgical treatment has been questioned, experienced surgeons achieve long term reflux cure rates of about 85-95%. Success with medical therapy is the only thing that predicts a successful surgical outcome. The only possible exception is in asthmatic patients where reduction of oral steroids was possible in a small series of Caucasian patients after surgery. Similar data from Asia are lacking. It is an option for patients who do not wish to take long term medications. Performance of bariatric surgery and fundoplication can also be done at the same time for patients with morbid obesity and GERD.

9. GERD and *H. pylori*

A negative correlation between GERD and *H. pylori* is observed in many Asian countries, suggesting a protective role of *H. pylori* against GERD. Although eradication of *H. pylori* may increase basal gastric acidity and reduce the efficacy of PPI therapy in some patients, the bacteria should still be eradicated to protect the patient from *H. pylori* associated gastric diseases.

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "On Gastro-oesophageal Reflux-Induced Diseases " by Dr. Ambrose CP Kwan, and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded 1 CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 March 2008. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please choose the best answer:

1. Which of the following symptoms or condition is not associated with GERD:
a. Chronic cough
b. Hoarseness of voice
c. *H.pylori*
d. Dental erosions
e. Globus

2. The pathophysiology of GERD may involve the following conditions except:
a. Excessive exposure of the oesophagus to acid and pepsin during transient lower oesophageal sphincter relaxation
b. Delayed oesophageal motility
c. Hiatus hernia
d. Accelerated gastric emptying
e. Decreased lower oesophageal sphincter pressure

3. The followings are new investigations or treatment for GERD except:
a. 48 hour wireless Bravo pH study
b. Oesophageal capsule endoscopy
c. 24 hour multi-channel intraluminal impedance for measurement of non acidic reflux
d. MRI oesophagus
e. Endoscopic photodynamic therapy for Barrett's oesophagus with high grade dysplasia

4. Potential benefits of endoscopy in GERD patients include:
a. Detect malignancy especially in patients with alarming signs and symptoms like anaemia, dysphagia or weight loss
b. Assess the severity of reflux oesophagitis
c. Diagnose Barrett's oesophagus
d. Narrow band imaging may detect areas of high grade dysplasia in patients with Barrett's oesophagus
e. All of the above

5. For GERD patients who do not respond to daily dose of proton pump inhibitors, the following actions are appropriate except:
a. Combine two proton pump inhibitors (PPI)
b. Add H2 blocker at nite time
c. Consider 24 hr pH study or Bravo wireless 48 hour pH study
d. Change the morning dose of PPI to 30 minutes before dinner
e. Step up the dose of PPI to b.d.

6. The following drugs are associated with oesophagitis except
a. Alendronate
b. Iron supplements
c. Aspirin
d. Potassium
e. Calcium

7. The following statements on relationship between *H.pylori* and GERD is correct except:
a. *H.pylori* infection is not associated with GERD.
b. Eradication of *H.pylori* may increase basal gastric output in some patients with GERD.
c. *H.pylori* should not be eradicated in patients with GERD.
d. Eradication of *H.pylori* may affect the potency of PPI drugs.
e. PPI therapy leads to migration of *H.pylori* from antrum to corpus.

8. The following statements on Barrett's oesophagus are correct except:
a. Barrett's oesophagus is a highly-malignant condition
b. Adenocarcinoma may arise from dysplastic lesion
c. Barrett's oesophagus is the replacement of normal squamous epithelium by metaplastic specialized columnar epithelium.
d. Biopsy should be taken to assess the presence and degree of dysplasia.
e. Chromo-endoscopy helps to identify areas of dysplasia

9. The following statements on treatment are correct except:
a. Endoscopic therapy for GERD is well established in Asia.
b. Results of laparoscopic fundoplication are best in patients who respond well to PPI therapy.
c. Bariatric surgery and laparoscopic fundoplication can be done at the same time for patients with morbid obesity and GERD.
d. Laparoscopic fundoplication offers an alternative form of therapy for patients who do not want to take long term medications.
e. Long term durability of laparoscopic fundoplication has been questioned and a subset of patients may need to undergo re-operation or restart on PPI therapy few years later.

10. The following statements are correct except:
a. Hip fracture is associated with long term PPI therapy
b. Risk of hip fracture is higher with high dose PPI therapy.
c. The incidence of adenocarcinoma of oesophagus is rising in HK.
d. Fatty foods, coffee, chocolate, alcohol and smoking are provocative factors.
e. The prevalence of GERD is rising in some Asian countries.

ANSWER SHEET FOR MARCH 2008

Please return the completed answer sheet to the Federation Secretariat on or before 31 March 2008 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

On Gastro-oesophageal Reflux-Induced Diseases

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1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Name (block letters):_____ HKMA No.: _____

HKID No.:___ ___ - ___ ___ ___ ___ X X (x)

Other Membership No. (please indicate): _____

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Answers to February 2008 issue

Management of Youth Substance Users in General Practice Settings

1. C 2. B 3. A 4. D 5. C 6. E 7. D 8. D 9. A 10. C

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Review on Inflammatory Bowel Disease in Hong Kong

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Inflammatory bowel disease (IBD), which encompasses Crohn's disease (CD) and ulcerative colitis (UC), is a spectrum of heterogeneous disorders with variable clinical manifestations and outcomes. It is thought to result from inappropriate and ongoing activation of the mucosal immune system driven by the presence of normal luminal flora.[1] Although IBD manifests throughout all ethnic groups, there has been marked heterogeneity in its incidence and prevalence, presumably due to genetic and environmental factors. IBD is rare in the Chinese population, but its incidence is on the rise.[2-3] This review will focus on the epidemiology of IBD in Hong Kong.

Little was known about IBD in Chinese before 1990s.[4] Case report describing CD in our population was first published in 1994.[5] In the past decade, incidence of CD has increased more than three-fold from 0.3 per 100,000 in 1989 to 1.0 per 100,000 in 2001.[2] The rate of rise was greatest in the mid to late 1990s. The cause of this rise remains uncertain but may involve environmental changes associated with urbanisation and Westernisation of the living standards, culture and diet. Leong's study was conducted at the Gastroenterology outpatient clinic of the Prince of Wales Hospital. Eighty-five percent of patients were born in Hong Kong and 15% were emigrants from southern mainland China. The population consisted of middle-income earners, with a median monthly income slightly higher than the median income for the whole of Hong Kong and 45% of people had received a tertiary (university or technical college) education. It is believed that a higher socioeconomic class may be implicated in the development of IBD.[6] The study was hospital-based, yet it reasonably reflected the regional population at that time because 94% of our population attended the public hospital system rather than to the private practice. The male to female ratio was 2.5:1. The mean age of diagnosis was 33.1 years with 78% of all patients presenting below the age of 40 years. The distribution of the age of onset was bimodal with the main peak of onset in the third decade, and a secondary peak in the sixth decade. The median time to diagnosis was nine months and the common symptoms at presentations were diarrhoea (65%), abdominal pain (65%), rectal bleeding (51%), and weight loss (45%). Extraintestinal manifestations were reported in 4% of CD patients upon diagnosis.

We have extended our former CD cohort[2] and prospectively collected clinical data since 2001.[7] Seventy-three out of the 109 (67%) patients started off with nonstricturing, nonpenetrating disease (B1) according to the Montreal Classification (MC) which was a new classification developed by the international working party in 2005 for more precise categorisation of CD. [Table 1][8] In MC, perianal disease was no longer an independent criterion for B3 category but became a disease modifier based on the fact that perianal CD was recognised to have a different natural history from intestinal penetrating disease with respect to disease progression and outcome. The proportions of patients with stricturing (B2) and penetrating (B3) disease at diagnosis as determined by the MC were 30.3 % and 2.8 % respectively.[7] CD behaviour changed significantly three years after diagnosis with an increase in the stricturing and penetrating phenotypes. The proportion of B3 increased from 2.8% to 14.3%, and B2 increased from 30.3 % to 42.9 % after ten years. In fact, phenotypic changes in CD also occurred in Chinese patients in the same way as Caucasian CD.[9-10] The non-stricturing, non-penetrating phenotype had a tendency to progress into stricturing or penetrating disease, whereas stricturing diseases rarely developed penetrating phenotypes. This would support the concept that CD consists of a heterogeneous group of disorders that eventually result in a specific phenotypic complication. Fifty-four percent of patients in our CD cohort had ileocolonic disease (L3). Thirty-five percent and eleven percent of patients had colonic (L2) and terminal ileal disease (L1) respectively. Interestingly, there was more upper gastrointestinal tract disease (L4) as defined by any disease location proximal to the terminal ileum (excluding the mouth) in the Chinese CD patients. The figure was reported to be as high as 19%.[2] Besides, the upper gastrointestinal location of CD often coexisted with L1 or L3 but never with the L2 location disease. This might be due to the Paneth cells being situated throughout the small bowel, which plays a vital role in secreting the inflammatory mediators for disease perpetuation. Disease location remained stable after ten years of follow up. The phenotype of CD patients reported by Lok and his group from the Tuen Mun Hospital was largely comparable to ours except that patients in the Lok's cohort (n=27) did not have L4 disease which might be due to the small number of patients or possibilities of inadequate small bowel investigation.[3] Thirty four patients (31.2%) in our CD cohort underwent major surgery during the follow up period and the Kaplan-Meier curve is shown in Figure 1.[7] Stricturing (P=0.002; adjusted HR: 3.3; 95% CI: 1.5-7.0) and penetrating (P=0.03; adjusted HR: 5.8; 95% CI: 1.2-28.2) phenotypes according to the MC were predictive of the need for major surgery. Colonic disease was found to be protective against major surgery (P=0.02; HR: 0.3; 95% CI: 0.08 - 0.8). One

plausible explanation is that colonic CD presentations such as hematochesia, abdominal pain and diarrhoea, might drive our Chinese patients to an earlier presentation and treatment which may delay the onset of complications and subsequent surgery. In small bowel disease, symptoms might not be prominent until significant stricture develops. Age at diagnosis did not correlate with surgery in our cohort and neither was the history of smoking associated with surgery. Unlike the Caucasians, ever smoking was not a risk factor in the development of CD. The odds ratio (OR) of ever-smokers in the development of CD compared with age and sex matched healthy controls was only 1.02 (95% CI: 0.5-1.9).[2] In fact, current or previous smoking was found to be protective against the development of granulomas.[11] Interestingly, only 2 of our CD patients had a definite family history of CD and were of a father and son relationship. IBD is likely to be a polygenic disease of variable penetrance that requires a complex interaction of genes with the environment for disease manifestation. Vertical and horizontal familial clustering of IBD is reported up to 40% in Caucasians. [12-13] This is in excess of the rate in Asian studies where the rate is 0-7%.[14] The CARD15/NOD2 single nucleotide polymorphisms (SNPs) associated with CD have been confirmed in multiple Caucasian studies. Among CD patients, carrying at least one high-risk gene polymorphism increased slightly the risk for familial disease (OR: 1.5, 95% CI: 1.2 - 1.9), predicted the stricturing behaviour (OR: 1.9, 95% CI 1.6 - 2.3), and small bowel location of disease (OR 2.5, 95% CI 2.0 - 3.2).[15] However, the prevalence of CARD15/NOD2 mutations in Chinese CD is negligible.[16-17]

The incidence of UC in our locality increased two-fold from 0.6 per 100,000 in 1986 to 1.2 per 100,000 in 2001.[2] There is evidence that the incidence continues to increase (unpublished data). In our UC cohort in which more than 170 patients have been recruited, the median age of diagnosis was 37 years. Extensive colitis was found in 42.4% of patients at diagnosis, followed by left-sided colitis (29.7%) and proctitis (27.9%). However, ulcerative proctitis was reported to be the commonest disease phenotype (38.4%), followed by extensive colitis (35.6%) and left-sided colitis (26.0%) by the group from another regional hospital.[18] Extra-intestinal manifestations occurred in 13.7% of patients. Four out of 73 (5.5%) patients underwent colectomy.

Our group conducted a study comparing the IBD-related knowledge, quality of life (QoL), and use of complementary and alternative medicines and therapies (CAMP) in Chinese and Caucasian IBD patients three years ago.[19] The overall use of CAMT was similar in both groups (33% of Chinese and 37% of Caucasian patients) and similar for CD and UC. We found that the IBD knowledge score was higher in Caucasian than in Chinese IBD patients and was independent of education and occupation. Twenty-one percent of Chinese patients incorrectly identified their IBD type as compared to 0% in the Caucasian group. However, QoL was higher in the Chinese than the Caucasian group, but not significantly different after adjusting for disease activity inferring that health-related QoL is unlikely to be greatly influenced by disease-related knowledge or education. Treatment of IBD has undergone revolutionary changes over the past ten years since the emergence of biologics which might alter the course of the disease. Although the treatment of IBD is beyond the scope of this review, certainly there are lots of interests in the treatment response in using those new agents among our Chinese IBD patients. Clinical trials on the treatment of IBD in our population are scarce but definitely needed.

There were a number of factors which have impeded the study of IBD in our locality in the past including the absence of an IBD registry, physician unawareness, and attendance to traditional Chinese herbalists. Efforts must be made to overcome all those obstacles and hopefully, in the forthcoming years, we can establish a comprehensive regional if not national registry of IBD patients so that more meaningful epidemiology studies can be carried out to facilitate our local health policy planning and promotion and help define the natural history of the disease in our population.

Table 1. The Montreal classification of Crohn's disease

Age at diagnosis	A1	16 yr or younger	
	A2	17-40 yr	
	A3	Over 40 yr	
Location	L1	Terminal ileum	L1+L4
	L2	Colon	L2+L4
	L3	Ileocolon	L3+L4
	L4*	Upper gastrointestinal tract	-
Behaviour	B1#	Non-stricturing non-penetrating	B1p†
	B2	stricturing	B2p
	B3	penetrating	B3p

**Upper gastrointestinal (GI) modifier (L4) allows for the co-classification of location L4 with L1 to L3*
† Perianal disease modifier (p)
#B1 category should be considered "interim" until a prespecified time has elapsed from the time of diagnosis.

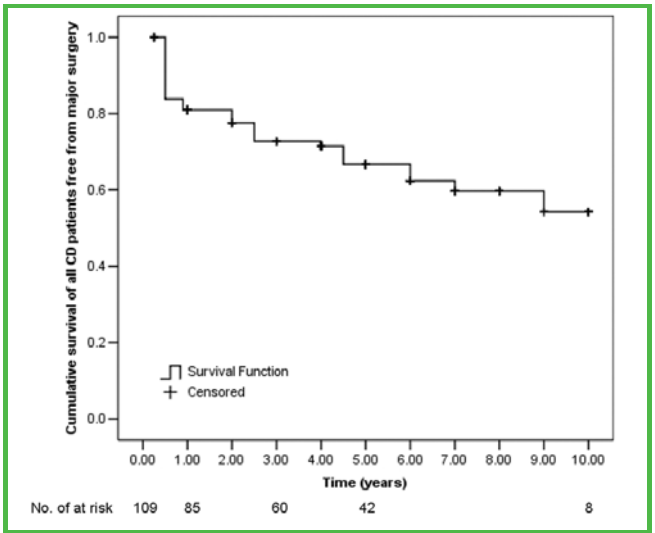

Figure 1. Cumulative survival of CD patients free from major surgery upon 10 years of follow-up.
Adopted from: Chow DK, Leong RW, Lai LH, et al. Changes in Crohn's disease phenotype over time in the Chinese population: Validation of the Montreal Classification System. Inflamm Bowel Dis 2007 [Epub ahead of print]

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Recent Advances in the Management of Nonalcoholic Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD) has emerged as the most common chronic liver disease in affluent countries. Due to the adoption of Western diet and lifestyle, there is also an epidemic of NAFLD in Asia. In Japan and Indonesia, the prevalence of NAFLD is as high as 30%.[1] In a population screening project in Shanghai, China, around 15% of the adults were also found to have NAFLD.[2] Necroinflammation and fibrosis are common in Asian patients with NAFLD, and progression in fibrosis occurs in up to 50%.[3-5] Progression to liver cirrhosis, liver failure and hepatocellular carcinoma has been reported. Besides, NAFLD patients have higher mortality than the general population, and the risk of cardiovascular diseases is doubled.[6,7] Therefore, heightened awareness and proper management of this disease are important.

NAFLD has close relationship with the metabolic syndrome. Assessment of NAFLD patients should include both the evaluation of the liver condition as well as the associated features of metabolic syndrome. Healthy lifestyle remains the cornerstone for the management of NAFLD. Pharmacological treatment is under intensive investigations. Bariatric surgery is reserved for patients with morbid obesity.

Clinical evaluation

Severity of liver disease

NAFLD can be roughly divided into simple steatosis and nonalcoholic steatohepatitis (NASH). Patients with simple steatosis run a benign course. On the other hand, patients with NASH tend to have progressive disease and increased mortality. One of the goals is to differentiate simple steatosis from more severe disease.

Traditionally, the assessment of NAFLD severity depends on histology.(Figure 1) However, liver biopsy is an invasive and expensive procedure. It carries a small but definite risk of bleeding, pneumothorax, haemothorax, and puncture of adjacent organs. Although liver biopsy has been considered the gold standard, emerging data challenged this concept. In one study, biopsies were taken from both the right and left lobe of the liver during bariatric surgery. Concordance was only 53% for liver fibrosis between the two samples, and even poorer for most features of necroinflammation.[8]

Due to the limitation of liver biopsy, there is strong interest in the development of non-invasive tests for liver fibrosis. They can be divided into serum biomarkers and elastography techniques.

The first development of non-invasive tests for liver fibrosis is to construct a formula including factors associated with fibrosis. The BARD, BARG, BAAT and HAIR scores were all developed for this purpose. The factors used in these scores include body mass index, age, AST/ALT ratio, ALT, diabetes, HbA1c, insulin resistance index, triglycerides and hypertension. Recently, a group of hepatologists from the United States, Europe and Australia reviewed the clinical data of 733 patients with biopsy-proven NAFLD and identified 6 factors independently associated with advanced liver fibrosis - age, body mass index, impaired fasting glucose or diabetes, AST/ALT ratio, platelet count and albumin.[9] The NAFLD fibrosis score was constructed from these 6 parameters, and high and low cutoff values were selected. When the score is below the low cutoff point (< -1.455 from the study), the sensitivity and negative predictive value are 82% and 93%, respectively. When the score is above the high cutoff point (> 0.676), the specificity and positive predictive value are 98% and 90%, respectively.

There are a few limitations to these prediction models. Firstly, none of the parameters chosen is a direct measurement of fibrogenesis or fibrinolysis. Secondly, fibrogenesis and fibrinolysis are dynamic process, while both the score and the 'gold standard' of liver biopsy are taken as a snapshot. Thirdly, the 'gold standard' of liver biopsy is also limited by sampling bias and intraobserver and interobserver variability. Therefore, it is unlikely that these prediction models will ever achieve close to 100% accuracy.

Fibroscan is a one-dimensional transient elastography. It is a rapid and non-invasive method to measure the stiffness of the liver. Early data show that the accuracy of Fibroscan is at least as good in NAFLD patients as in patients with other chronic liver diseases. In 67 Japanese NAFLD patients, the sensitivity, specificity, positive and negative predictive values of Fibroscan to exclude stage 3 and 4 fibrosis (optimal cutoff 8 kPa) were 88%, 84%, 64% and 96%, respectively.[10] However, it is important to note that the success rate of Fibroscan is lower in obese patients, who often harbour NAFLD.[11] In patients with thick subcutaneous fat, Fibroscan may fail to acquire any reading because ultrasound waves cannot penetrate deep enough.

Metabolic syndrome

Apart from evaluating the severity of liver injury, clinicians should not ignore common comorbid illnesses. The Metabolic syndrome is closely associated with NAFLD.[12] As a minimum, anthropometric measurements, blood pressure, fasting glucose and

lipids should be checked. Both the body mass index and waist circumference are used to assess the degree of obesity. In particular, waist circumference is a reflection of central obesity and is strongly associated with the risk of myocardial infarction.[13] Moreover, people of different ethnicity develop complications of metabolic syndrome at different body mass indices.[12] Therefore, the definition of obesity is different in different ethnic groups. In Chinese, normal waist circumference is below 90 cm in men and 80 cm in women.[14] In Asia, people with body mass index above 23 kg/m2 are considered increased risk and those above 27.5 kg/m2 are considered high risk.[15] The definition of metabolic syndrome by the International Diabetes Federation also takes ethnic differences into account (Table 1).[14]

The diagnosis of diabetes is made if the fasting plasma glucose is ≥ 7.0 mmol/l or the 2-hour plasma glucose is ≥ 11.1 mmol/l using a 75-gram oral glucose tolerance test.16 However, the American Diabetes Association discouraged performing oral glucose tolerance test because of cost and inconvenience. When oral glucose tolerance test was performed in NAFLD patients without history of diabetes, however, impaired glucose tolerance and diabetes were found in 29% and 33%, respectively.[17] Moreover, post-challenge hyperglycaemia strongly predicted the presence of advanced liver fibrosis. According to the current guideline of the Asia-Pacific Working Party on NAFLD, oral glucose tolerance test should be considered in NAFLD patients.[18, 19]

Cardiovascular diseases

In addition to the association with metabolic syndrome, NAFLD also has close relationship with cardiovascular disease. Among 85 male volunteers in Italy, subjects with hepatic steatosis had significantly higher carotid intima-media thickness than those without steatosis (0.94 ± 0.12 mm vs. 1.18± 0.14 mm, $p<0.001$).[20] The vasodilatory response of the brachial artery in response to ischaemia, a test of endothelial function, is also impaired in NAFLD patients.[21] The strongest evidence for the association between NAFLD and cardiovascular disease came from the Valpolicella Heart Diabetes Study. Two thousand one hundred and three type 2 diabetic outpatients were followed up for a median of 6.5 years. After adjustment for sex, age, smoking, diabetes duration, HbA1c, LDL cholesterol and medications, NAFLD remained an independent factor predicting incident cardiovascular disease (hazard ratio 1.96, 95% confidence interval 1.4-2.7, $p<0.001$).[7] Therefore, evaluation of NAFLD patients should include enquiry of symptoms and history of cardiovascular diseases. In positive cases, appropriate investigations should be arranged.

Treatment

Lifestyle management

Like most metabolic diseases such as type 2 diabetes and obesity, lifestyle modification remains the cornerstone of NAFLD treatment. In animal models, diets rich in olive oil, fish oil and fibre appear to improve hepatic steatosis.[22-24] In one human study, 9 of 15 NASH patients undergoing 1 year of intense dietary intervention had histological improvement.[25] The diet selected in that study was as follows: 40-45% of daily calories from carbohydrates with an emphasis on complex carbohydrates with fibre; 35-40% fat with emphasis on mono- and polyunsaturated fats; and 15-20% protein. It is however noteworthy that only 16 of 23 patients completed 12 months of dietary intervention, and only 15 had paired liver biopsies. This is a typical phenomenon in most lifestyle intervention studies. How one can achieve good compliance remains a major challenge to clinicians and allied health staff.

In another study involving 25 obese Japanese NAFLD subjects, diet restriction and exercise (walking or jogging) for 3 months resulted in improvement in metabolic parameters and liver histology.[26] In 348 male employees with elevated ALT found during annual health checkup, weight loss and regular exercise were associated with ALT normalisation one year later.[27]

While there is ample observational data showing that diet and exercise are beneficial for NAFLD patients, it is difficult to recommend the optimal dose and type. Further studies are required.

Pharmacological treatment

Drug treatment of NASH is under intense investigation. The studied drugs are acting on various targets central to the pathogenesis of NASH: insulin resistance, lipid metabolism, oxidative stress, inflammation, fibrosis, etc.

The drugs that have attracted most attention are insulin sensitisers. Metformin was the first insulin sensitiser used to treat NASH. In a single-arm study involving 20 NASH patients, metformin 500 mg three times a day for 4 months resulted in ALT normalisation in 50% of the patients and improvement in insulin sensitivity.[28] Subsequently, an open label, randomised trial showed that patients treated with metformin (2 g per day for 12 months) had a higher rate of ALT normalisation than controls.[29] Metformin treatment also resulted in improvement in hepatic steatosis, inflammation and fibrosis. Unfortunately, only 17 patients receiving metformin had paired liver biopsies, and histological results of the control group were not presented.

Thiazolidinediones (pioglitazone and rosiglitazone) are another class of insulin sensitiser tested in NASH patients. In uncontrolled studies, both rosiglitazone and pioglitazone treatment for 12 months resulted in histological improvement in up to two-third of patients.[30, 31] Recently, a randomised controlled trial on pioglitazone has been completed. Fifty-five NASH patients with impaired glucose tolerance or type 2 diabetes were randomised to receive pioglitazone 45 mg daily or placebo for 6 months.[32] The pioglitazone group had decreased ALT levels, increased hepatic insulin sensitivity, and improved hepatic steatosis, ballooning necrosis and inflammation. However, the beneficial effect was not durable. When pioglitazone was stopped, serum ALT and total hepatic fat worsened again.[33] Therefore, NASH patients will need long-term therapy if this drug is approved for this indication. Another problem of thiazolidinedione treatment is weight gain. In NASH patients treated with pioglitazone for 6 months, the average weight gain was 2.5 kg.[34] When further tests were performed, increase in whole body fat was found to be the main cause of weight gain. This casts doubt on the long-term safety of the drug. Indeed, although several meta-analyses provided conflicting

data, there was concern over the cardiovascular safety during long-term rosiglitazone treatment.[35]

Since oxidative stress is pivotal in the pathogenesis of NASH, anti-oxidants have also been tested. In a double-blind, randomised controlled trial involving 45 NASH subjects, vitamin E and vitamin C resulted in some improvement in liver fibrosis, but not in ALT normalisation or necroinflammation.[36]

Ursodeoxycholic acid has been commonly used to treat primary biliary cirrhosis and other causes of cholestasis. In the largest clinical trial on NASH to date, 166 NASH patients were randomised to receive ursodeoxycholic acid or placebo for 2 years.[37] However, ursodeoxycholic acid failed to demonstrate any superiority over placebo in all biochemical and histological assessments.

Other investigational therapies include phlebotomy, anti-inflammatory drugs (e.g. pentoxifylline, etanercept, infliximab, thalidomide, misoprostol), probiotics, betaine and pancaspase inhibitors. They need to be better evaluated in properly designed clinical trials.

Since NAFLD patients often have dyslipidaemia, one important question is whether lipid lowering drugs are safe in these patients. Among 68 NAFLD patients followed up for 10.3 to 16.3 years, statin use was found to be safe and not to cause histological deterioration.[38] In another observational study involving 166 chronic hepatitis C patients on statin, 332 chronic hepatitis C patients not on statin, and 332 patients on statin but without hepatitis C infection, statin use in chronic hepatitis C patients was associated with mild-to-moderate ALT elevation, but not severe liver dysfunction.[39] Recently, a randomised controlled trial included 326 patients with hypercholesterolaemia and chronic liver disease.[40] NAFLD was present in 64% and chronic hepatitis C in 23%. The patients were randomised to receive pravastatin 80 mg daily or placebo for 36 weeks. Not surprisingly, pravastatin was effective in lowering the total cholesterol, LDL cholesterol and triglycerides. Moreover, fewer patients in the pravastatin group had doubling of ALT or ALT rising above 2 times the upper limit of normal than controls. All data support the safety of statin in patients with chronic liver disease. Current guideline also does not find close monitoring of liver function tests during statin therapy meaningful.[19]

Bariatric surgery

Bariatric surgery is effective in achieving weight reduction. Long-term mortality was significantly lowered in patients with morbid obesity undergoing bariatric surgery than those on usual medical care.[41, 42] There was early concern that rapid weight loss might increase liver fibrosis in NAFLD patients. However, recent data showed that the risk is low if there was only modest weight loss and less malnutrition. Some observational studies also found improvement in steatosis, inflammation and fibrosis in NASH patients after bariatric surgery.

Conclusion

In summary, NAFLD is increasing in incidence. Although only a minority of NAFLD subjects eventually dies of liver complications, the absolute number is expected to be huge because the total number of NAFLD subjects is large. Serum biomarkers and transient elastography are potential non-invasive tests for liver fibrosis in NAFLD patients. Lifestyle modification is the most important management. Insulin sensitisers hold much promise as the pharmacological treatment of NASH, but long-term data are required. Statins and bariatric surgery are both safe in NAFLD patients, and should be provided if there is clinical indication.

Table 1. Metabolic syndrome definition by the International Diabetes Federation[14]

Central obesity
Waist circumference (ethnicity specific)
Plus any two:

Raised triglycerides
>1.7 mmol/l
Or specific treatment for this lipid abnormality

Reduced HDL-cholesterol
<1.03 mmol/l in men
<1.29 mmol/l in women
Or specific treatment for this lipid abnormality

Raised blood pressure
Systolic ≥130 mmHg
Diastolic ≥ 85 mmHg
Or treatment of previously diagnosed hypertension

Raised fasting plasma glucose
Fasting plasma glucose ≥ 5.6 mmol/l
Or previously diagnosed type 2 diabetes
If above 5.6 mmol/l, oral glucose tolerance test is strongly recommended

Ethnicity specific definition of central obesity

Ethnic group	**Waist circumference**
Europeans	
Men	≥ 94 cm
Women	≥ 80 cm
South Asians and Chinese	
Men	≥ 90 cm
Women	≥ 80 cm
Japanese	
Men	≥ 85 cm
Women	≥ 90 cm

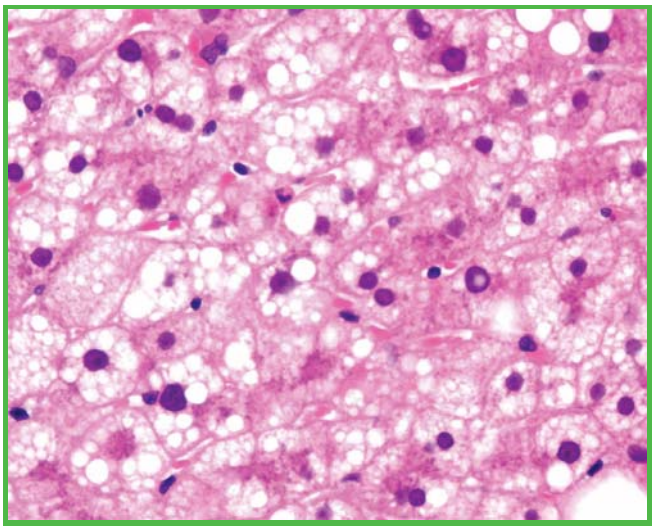

Figure 1. NAFLD is characterised by macrovesicular steatosis.

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Drug-induced Liver Injury: An Update

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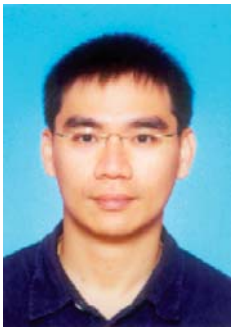

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Introduction

The liver is a major organ for metabolism of foreign substances and also functionally interposed between the site of resorption and the systemic circulation. These conditions render the liver not only the most important organ for detoxification of foreign substances but also a major target of their toxicity. More than 1000 drugs have been associated with idiosyncratic hepatotoxicity and drug-induced liver injury (DILI) is the main reason for removing approved medications from the market. Moreover, drug-induced hepatotoxicity contributes to more than half of the cases of acute liver failure, with paracetamol being the principal offending agent in western countries. In Sweden, hepatic injury due to drugs occurred in 2.3% of patients hospitalised for jaundice[1]. However, the real incidence of DILI remains unknown because of the difficulty in establishing diagnosis and the low reporting frequency to the pharmacovigilance authorities[2]. DILI represents a clinical challenge due to the large number of reported hepatotoxic drugs in current use, the broad spectrum of hepatic injuries by which it may manifest and the frequent absence of clinical findings that permit its diagnosis with certainty. Delay in the diagnosis of DILI may result in unnecessary extensive investigations and poor patient outcomes including acute liver failure and cirrhosis. The purpose of this review is to discuss the causality assessment of DILI in clinical practice and update the recent advances in the understanding of hepatotoxicity of some commonly used drugs and herbs, especially among patients with underlying liver disease.

Patterns of drug-induced liver injury

Hepatotoxicity may be predictable or unpredictable. Predictable reactions typically are dose-related and occur with short latency (within a few days) after some threshold for toxicity is reached. Paracetamol (acetaminophen) is a classic example. Conversely, idiosyncratic reactions occur with variable, sometimes prolonged latency (1 week to 1 year), with low incidence and, may be or may not be dose-related. On the basis of the alanine aminotransferase (ALT) and alkaline phosphatase (ALP) levels, the liver test abnormalities are classified into hepatocellular, cholestatic, and mixed patterns. Hepatocellular injury is characterised by the marked elevation of ALT level, usually preceding increase in total bilirubin level and modest increase in ALP level. The elevation of ALT level tends to resolve over the course of several weeks after discontinuation of the offending agent. Sometimes asymptomatic liver test abnormalities resolve despite continued drug use, a phenomenon referred to as adaptation.

Cholestatic injury involves a predominantly increase in ALP level as a result of canalicular cholestasis or ductular injury. It is usually not as life-threatening as hepatocellular injury, but it may lead to chronic ductopenia and rarely cirrhosis. In a mixed pattern of DILI, patients present with a combination of acute hepatitis and cholestasis. Of the three patterns of liver injury, hepatitis is more commonly accompanied by acute liver failure. In a Spanish registry, more than 10% of patients with drug-induced hepatocellular injury and jaundice may progress to death or requiring liver transplantation. The combination of coagulopathy and encephalopathy occurring within 26 weeks after the onset of illness in a patient without pre-existing cirrhosis carries a poor prognosis in the absence of liver transplantation.

Causality assessment of DILI

The presentation of DILI ranges from asymptomatic elevation of ALT level to acute liver failure and may mimic all forms of acute and chronic liver disease. High index of suspicion is paramount especially in patients using prescription or nonprescription medication or even dietary supplements. Other causes of liver disease must be ruled out. In appropriate clinical settings, sepsis-induced cholestasis and liver injury due to heart failure or "shock liver" should be considered. The hepatic dysfunction due to some non-drug causes is summarised in Table 1.

The Roussel Uclaf Causality Assessment Method (RUCAM) is the most widely-used methods for assessing non-organ-specific drug reaction to well-defined hepatic reactions[3]. The RUCAM is based on 7 major criteria, namely (1) time to onset, (2) course of the reaction, (3) risk factors for the reaction, (4) assessing the role of concomitant therapies, (5) screening for non-drug-related causes, (6) weighing the information known about the DILI in question, and (7) confirmation of the reaction by positive rechallenge or in vitro assays. A causal relationship is graded as: excluded, unlikely, possible, probable, and highly probable. Liver biopsy is not considered as a diagnostic criterion for DILI as most of the histological changes may be non-specific and provide only circumstantial evidence that a drug is involved. Therefore biopsy is reserved for patients who have acute injury that fails to resolve or alternative diagnosis is suspected.

Table 1 Common non-drug causes of liver impairment

Aetiologies	Diagnostic tests
Viral hepatitis	
Hepatitis A virus	HAV Ig M
Hepatitis B virus	HBc IgM and HBs Ag
Hepatitis C virus	Anti-HCV antibodies, HCV RNA
Hepatitis E virus	HEV IgM
Biliary tract diseases	Abdominal ultrasonography, ERCP, MRCP
Alcohol	Gamma glutamyltransferase
Autoimmune diseases	
Autoimmune hepatitis	Type 1: anti-smooth muscle antibodies, anti-nuclear factor Type 2: anti-liver kidney-microsomal antibodies
Primary biliary cirrhosis	Anti-mitochondrial antibodies
Haemodynamic disorders	
Heart failure	Echocardiography
Ischaemia/ hypoxia	Clinical scenario
Budd-Chiari syndrome	Doppler ultrasound
Portal vein thrombosis	Doppler ultrasound
Veno-occlusive disease	Liver biopsy
Metabolic/ genetic diseases	
Wilson's disease	Diminished serum ceruloplasmin, elevated urinary and serum copper
Haemochormatosis	Elevated iron saturation and ferritin levels
Sepsis-induced cholestasis	Sepsis work-up

Common hepatotoxic agents

Paracetamol

The most commonly implicated drugs involved in acute liver injury and their disease patterns are summarised in Table 2. Paracetamol poisoning is the leading cause of drug-induced fulminant hepatitis in the United States. Traditionally, it is believed that a minimum of 7.5 - 10g of paracetamol is needed to produce hepatic necrosis in an adult. In the analysis of acute paracetamol-induced hepatotoxicity of the Acute Liver Failure Group in the United States[4], a median dose of 24g was ingested with 44% of the cases due to an intentional (suicidal) overdose. However, they found one patient who developed liver failure after taking only 1.2g of paracetamol, which is barely above a single therapeutic dose. It is possible that paracetamol (in non-toxic doses) may act as a cofactor with viral hepatitis or other medications to produce acute liver failure - a so-called 'dual pathology' scenario. Indeed, old age, the presence of underlying liver disease, poor nutritional status and the combination use of alcohol and opiates with paracetamol are all risk factors for paracetamol poisoning. Furthermore, long-term (about 1 year) exposure to paracetamol (3-4g daily) can also lead to chronic liver injury.

Interestingly, paracetamol poisoning appears less common among Chinese and it is possibly due to the different habit of drug usage between Chinese and Caucasians. A pharmacokinetics study from our locality[5] showed that Chinese subjects appeared to be better protected against paracetamol hepatotoxicity by having more rapid absorption of paracetamol, as well as a tendency to produce less toxic metabolites. However, further studies about the possible ethnic differences in paracetamol metabolism are needed before definitive statements can be made.

Table 2. Commonly-reported drugs associated with drug induced liver injury (DILI)

Drugs associated with DILI
Paracetamol
Non-steroidal anti-inflammatory drugs Diclofenac Ibuprofen Naproxen
Antibiotics Amoxicillin/ clavulanate (augmentin) Flucloxacillin Erythromycin Ciprofoxacin Anti-tuberculosis drugs (Isoniazid, rifampicin, pyrazinamide) Anti-retroviral drugs (e.g. ritonavir)
Immunosuppressants Azathioprine Cyclophosphamide
Anti-arrthymia drugs Amiodarone
Anti-epileptics Phenytoin Carbamazepine Valproic acid
Psychiatric drugs Chlorpromazine Paroxetine

Augmentin (amoxicillin/ clavulanic acid)

According to various registries and retrospective studies in European countries and the United States, antibiotics (including anti-tuberculosis drugs) are the most common agents causing DILI followed by non-steroidal anti-inflammatory drugs (NSAIDS), with diclofenac most often responsible for the DILI[6]. It is worth mentioning that amoxicillin/clavulanic acid (augmentin) is the most frequently reported antibiotic associated with DILI. The estimated risk of symptomatic hepatitis due to augmentin is <1 in 100,000 persons exposed. Interestingly, age is found to be the most important determinant in the biochemical expression of augmentin-induced hepatotoxicity[7]. Patients younger than 55 years of age exhibit predominantly hepatocellular damage, which occurs at 1 week after exposure to the drug while cholestatic liver injury occurs mostly at 2-3 weeks and the mixed liver injury proportionally predominates after 3 weeks. In a prospective study by Andrade et al. in Spain, they reported that 13% (59/446) of their in- and out- patients suffering from acute DILI were due to augmentin and 6% of them developed acute liver failure or progressed to chronic liver disease and cirrhosis[8] This brings into the question the generally-held opinion that the clinical outcome of hepatotoxicity caused by augmentin is invariably toward recovery.

Anti-tuberculosis drugs

Approximately 10-20% of patients receiving isoniazid will develop mild to moderate elevation of ALT and about 0.1% develops clinical hepatitis. Slow acetylator status and genetic polymorphism of CYP2E1 have been identified as risk factors. The concomitant intake of rifampicin or pyrazinamide significantly increases the

risk of liver disease to 2-4%, which can be partly explained by an induction of CYP450 enzymes.

There is a continuous interest in hepatitis B as a risk factor for anti-tuberculosis drugs-related hepatotoxicity. In 1990, a Taiwan study[9] showed that 2.4% of patients treated with isoniazid, rifampicin and ethambutol developed symptomatic hepatitis of which, more than 35% were hepatitis B carriers and about half of them developed liver failure subsequently. In contrast, the mortality rate for non-hepatitis B carriers was less than 4%. Recent studies have shown that about 35-59% of hepatitis B carriers will develop abnormal liver function tests during anti-tuberculosis treatment and 25-50% of them are symptomatic.

Thus, it is recommended that a baseline clinical and laboratory evaluation, including liver function and hepatitis B surface antigen, should be performed before the start of anti-tuberculosis treatment. And patients should be taught to recognise symptoms of hepatitis and to report them promptly. Patients with risk factors for hepatotoxicity for example, those with preexisting liver diseases, the alcoholics, the elderly and malnourished should have their liver function monitored regularly. In fact, a study from India[10] has shown that periodic biochemical monitoring in patients receiving anti-tuberculosis therapy allowed for early detection of hepatotoxicity at an early stage and reintroduction of therapy was successful in nearly all patients after initial recovery. According to the Consensus statement of Department of Health and Hospital Authority in Hong Kong in 2002, anti-tuberculosis treatment should be withheld if ALT > 3x of upper limit of normal (ULN) or bilirubin is greater than 2x ULN and non-hepatotoxic regimen (based on streptomycin, ethambutol and fluoroquinolone) may be reintroduced when ALT level <2x ULN. Potential hepatotoxic drugs can be reintroduced sequentially once liver function is normal. Whether anti-viral therapy for hepatitis B infection reduces the risk of developing anti-tuberculosis drug-related hepatotoxicity remains uncertain. We have reported a successful case of reintroduction of isoniazid and rifampicin after adding lamivudine in a chronic hepatitis B patient[11]. Large-scale prospective studies are warranted to address this important clinical question.

Anti-diabetic drugs

Thiazolidinediones

Thiazolidinediones are insulin-sensitising agents used to treat diabetes mellitus through activation of the gamma isoform of the peroxisome proliferators-activated receptor (PPAR). Troglitazone, the first approved Thiazolidinediones, was withdrawn from the market in 2000 following 94 reported cases of liver failure. An idiosyncratic mechanism of toxicity was suggested based on the delayed onset of ALT elevation and a lack of dose effect. Rosiglitazone and pioglitazone were introduced into the market by the time troglitazone was withdrawn and both did not show an increased risk of ALT elevation in early clinical trials. Chalasani et al.[12] also showed no difference in the rate of ALT elevation between diabetics with and without elevated baseline ALT level after taking rosiglitazone, suggesting that diabetics with elevated baseline ALT are not at a higher risk of hepatotoxicity from rosiglitazone. Indeed, a significant proportion of diabetic patients with abnormal liver tests at baseline had a decrease in ALT while taking rosiglitazone, which is probably due to the improvement in underlying fatty liver disease while discontinuing pioglitazone in patients with nonalcoholic steatohepatitis (NASH) may result in subsequent elevation in ALT levels and worsening of liver parenchymal inflammation[13]. On the other hand, case reports of granulomatous hepatitis, cholestatic liver injury and fulminant liver failure due to rosiglitazone or pioglitazone have been reported. It is therefore advisable that thiazolidinediones should not be withheld in diabetics with minor liver dysfunction (ALT < 2.5x ULN) in the setting of NASH, especially given the potential beneficial effects, but it is prudent to monitor liver function tests during therapy.

Statin

Statins, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, are commonly used for hyperlipidaemia and form an important part of a preventative strategy against cardiovascular morbidity and mortality. Asymptomatic mild ALT elevation is a class effect of statins, and it does not indicate liver dysfunction. The incidence of ALT > 3x ULN associated with the use of statins is 0-3% and the rate has shown to be comparable with placebo in several trials. Clinically significant hepatotoxicity caused by statins remains extremely rare. Hepatocellular, cholestatic, and mixed patterns of liver injury have been reported in the literature. So far, there is no evidence to support routine monitoring of liver enzyme levels in patients receiving statins as it may result in high false-positive rates and unnecessary discontinuation of a drug that might be otherwise beneficial.

Although not evidence-based, current recommendations discourage the use of statins in patients with pre-existing liver disease. But this practice is problematic, because hyperlipidaemic patients have a significant prevalence of underlying NASH resulting in an elevated ALT level. Patients who have NASH would benefit from statins because of their heightened risk of cardiovascular disease. Furthermore studies showed that patients with compensated hepatitis C infection or primary biliary cirrhosis were not at higher risk for statin hepatotoxicity. Emerging data, in fact, suggest that statins are actually beneficial in patients who have underlying liver disease[14]. Thus, the Liver Expert Panel has made recommendations to the National Lipid Association that the presence of chronic liver disease and Child's A cirrhosis should not be considered as a contraindication for statin use, and that the current evidence supports the use of statins to treat hyperlipidaemia in patients with NASH[15].

Herbal products

Herbal medicine is widely used for the treatment of many common diseases in western countries as well as in Hong Kong. About 10% of adults in Hong Kong have consulted traditional Chinese medicine doctors and

13.5% have been using traditional Chinese medicine drugs. In a local survey[16], 32% of chronic hepatitis B patients have received traditional Chinese medicine. Herbal medicine is usually believed as 'natural', harmless and without side-effects. However a German study[17] showed that 0.9% of patients on Chinese herbal medicine had a more than 2-fold elevation of ALT level. A prospective study from Queen Mary Hospital showed that 7 of 45 (15.6%) chronic hepatitis B patients developed liver dysfunction attributable to traditional Chinese medicine and 3 of them developed liver failure resulting in death or requiring liver transplantation[18]. The common Chinese herbal medicines with potential hepatotoxicity are listed in Table 3. Diagnosing herb-induced hepatotoxicity is a major challenge to clinicians and sometimes impossible in some cases. Many patients often do not disclose the use of herbal medicines spontaneously and physicians should make specific inquiries about the use of herbal medicine. Many herbal formulae contain a list of different herbs of different dosages which make us difficult to impute the toxicity to a single herb. The amount of the herbs taken by patients, the possible interactions between different herbs and western medicines, the synergistic hepatotoxicity of herbal preparations, and risk factors of patients have to be considered. Additional problems with formulation of herbal medicines include botanical misidentification, product contamination or adulteration, and mislabelling and variability in the collection and extraction processes.

Table 3. Some common Chinese herbal medicine associated with hepatic dysfunction

Chinese Name	Plant/Component
千里光	Herba Senecionis Scandentis
川楝子	Fructus Toosendan
五倍子	Galla Chinensis
及己	Radix Chloranthi Serrati
天花粉	Radix Trichosanthis
石榴皮	Pericarpium granati
魚膽	Fish gallbladder
黃藥子	Tuber Dioscroeae Bulbiferae
雷公藤	Tripterygium wilfordii Hook
蒼耳子	Fructus Xanthii
喜樹	Fructus seu Radix Camptothecae Acuminatae
蜈蚣粉 (川足)	Dried centipede
石蠶	Germander (Teucrium chamaedrys)
金不換	Lycopodium serratum
麻黃	Ephedra sinica
小柴胡湯 (柴胡，半夏，生薑，黃芩，大棗，人參，甘草)	Xiao-chai-hu-tang (Bupleurum falcatum, Scutellaria baicalensis, etc.)
胡薄荷油	Pennyroyal oil (pulegone)
虎杖	Rhizoma Polygoni Cuspidati

Conclusions

Drug-induced liver diseases mimic various forms of liver injury that range in severity from transient, asymptomatic elevation in ALT levels to fulminant liver failure. The diagnosis of DILI is predicated on the exclusion of other possible causes and on the identification of a clinical signature that consists of the pattern of liver test abnormality, the duration of latency to symptomatic presentation, and the response to drug withdrawal. Administration of drugs in patients with underlying liver disease involves a balanced assessment of risk-benefit ratios that may favour judicious use when clear indications are present, as in the case of statins. Further studies are needed to provide better understanding of the pathogenesis and susceptibility to drug-induced liver injury which may in turn facilitate the prediction of human toxicity and provide better biomarkers for diagnosing DILI.

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Upper Gastrointestinal Bleeding During Anti-platelet Therapy

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Introduction

Anti-platelet therapy is effective in reducing the incidence of cerebrovascular accident, myocardial infarction and death from vascular causes in individuals with symptomatic atherothrombotic diseases.[1] Low-dose aspirin is most commonly used for the secondary prevention of vascular events. However, its use is frequently associated with adverse gastrointestinal events, which ranged from mild dyspepsia (31%) to life-threatening bleeding or perforation from peptic ulcer (3.1%) over a study period of 4 years in the UK Transient Ischaemic Attack study.[2] The elderly are regarded as a high-risk group. Clinically evident gastrointestinal bleeding occurred in 3% of elderly patients (70 years of age or older) receiving 100 mg of daily aspirin for 12 months.[3]

Clopidogrel (Plavix, Bristol-Myers Squibb Co.), another form of antiplatelet agent, has been approved by the Food and Drug Administration for use in secondary prevention of heart attacks and stroke[4]. Clopidogrel, a thienopyridine derivative similar to ticlopidine inhibits platelet aggregation through a different mechanism from aspirin. Aspirin inhibits platelet aggregation by irreversibly blocking the enzyme cyclooxygenase. This is essential for the synthesis of thromboxane A2, a substance which causes vasoconstriction and amplifies the platelet activation process leading to platelet aggregation[5]. By contrast, the thienopyridines inhibit platelet aggregation by irreversibly inhibiting the binding of adenosine diphosphate, a substance released from platelets during activation that amplifies the aggregation process. Thienopyridines do not impair the prostaglandin-dependent mucosal protective and ulcer healing mechanism, which is a side effect of aspirin.

This review aims to investigate the role of clopidogrel in patients with a history of peptic ulcers or erosions and to examine upper gastrointestinal bleeding in patients receiving aspirin and clopidogrel co-therapy. Since long-term proton pump inhibitors are widely prescribed in the prevention of antiplatelet induced peptic ulcer complications, its long-term safety is briefly reviewed.

Clopidogrel alone in patients with history of bleeding peptic ulcer is unsafe

The clinical efficacy of clopidogrel in secondary prevention of coronary heart disease, peripheral vascular disease and ischaemic stroke is demonstrated to be marginally more effective than aspirin in a randomised controlled clinical trial [Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE)][6]. The incidence of severe adverse upper gastrointestinal (GI) events was significantly lower for clopidogrel than aspirin (dyspepsia 0.97% versus 1.22% $p<0.05$; severe GI haemorrhage 0.52% versus 0.72%; $p<0.05$). Therefore, clopidogrel is safer than aspirin in average-risk patients, although the number needed to be treated by clopidogrel to prevent one excess aspirin-induced severe GI bleeding was 500. Indeed, in healthy volunteers without endoscopic gastroduodenal disease at baseline, an 8-day course with clopidogrel (75 mg/day), in contrast to aspirin (325 mg/day), did not induce any erosions on repeat endoscopic examination[7].

Since clopidogrel causes less GI bleeding than aspirin in average-risk patients, can clopidogrel replace aspirin in higher risk patients with peptic ulcer disease? In patients with active bleeding peptic ulcer, clopidogrel is definitely contraindicated[8]. In patients with previous peptic ulcer, there have been one retrospective study and two prospective randomised controlled studies on the safety of replacement of aspirin by clopidogrel therapy. In a retrospective study (n=70)[9] , 9 (12%) patients developed gastrointestinal bleeding after clopidogrel therapy for a median follow-up of one year. Clopidogrel-associated GI bleeding was significantly more common in patients with a history of GI bleeding associated with the use of aspirin or *H. pylori* infection than in those without (22% versus. 0%, p=0.007). Previous history of GI bleeding was the only independent predictor of clopidogrel-associated rebleeding. All except one lesion found during rebleeding were identical to the previous lesions, suggesting that impaired haemostasis from clopidogrel therapy might precipitate bleeding from an unhealed or relapsed ulcer. However, rebleeding occurred in none of the patients receiving a proton pump inhibitor. Hence, clopidogrel treatment alone may not be safe in high-risk patients and concomitant long-term proton pump inhibitor prophylaxis should be considered in this setting. Subsequently, this was followed by two randomised controlled studies. The first study recruited patients who took aspirin to prevent vascular events and presented with ulcer bleeding (n=320)[10]. After ulcer healing and eradication of *H. pylori* (if infected), patients were randomised to receive either clopidogrel (75 mg daily) plus placebo or aspirin (80 mg daily) plus esomeprazole (20 mg twice daily) for 12 months. The cumulative incidence of recurrent bleeding was significantly higher in the clopidogrel group (8.6 %), as compared to the aspirin plus esomeprazole group (0.7 %)

(absolute difference, 7.9 %; 95 % confidence interval, 3.4 to 12.4; p=0.001). There was a high rate of recurrence at the previous location (71 %). The second study recruited 170 patients with history of aspirin related ulcer bleeding[11]. The design was similar to that of the first study apart from using a smaller dose of esomeprazole (20 mg daily). During a follow-up of 52 weeks, the cumulative incidences of recurrent ulcer complications were 0% in patients receiving esomeprazole and aspirin and 13.6% in patients receiving clopidogrel (absolute difference, 13.6%; 95% confidence interval for the difference, 6.3-20.9; P = 0.0019). The results of these two randomised controlled studies suggest that aspirin plus esomeprazole is superior to clopidogrel alone in the prevention of recurrent ulcer bleeding among patients with a history of aspirin-induced ulcer bleeding.

Continuation of aspirin with proton pump inhibitor or conversion to clopidogrel with proton pump inhibitor is safe in moderately severe peptic ulcer disease

In patients with low-dose aspirin induced symptomatic peptic ulceration, what is the best initial treatment? By analogy with trials using full-dose conventional non-steroidal anti-inflammatory drugs, our current practice is to prescribe a proton pump inhibitor while continuing aspirin in patients without severe gastrointestinal bleeding. Although discontinuation of aspirin during the period of ulcer healing may offer a theoretical advantage, there is always a potential of precipitating an ischaemic vascular event, particularly in high-risk patients with unstable angina[12,13].

In a randomised controlled study[14], patients (n=129) with aspirin induced peptic ulcer disease treated with omeprazole (20mg/day) were randomised to receive clopidogrel or to continue with low-dose aspirin. Before randomisation, around 40% of patients in each group had minor gastrointestinal bleeding. These patients had small ulcers without adherent clot or visible vessels or patients with moderately severe gastro-duodenitis. Clopidogrel and aspirin were re-started after 0.86 and 0.44 days after upper endoscopy respectively. The result of this study demonstrated the incidence of unhealed ulcers or erosions at the 8th week was similar in both groups (converted to clopidogrel plus omeprazole 6% versus. continue aspirin 5%). Furthermore, no patient in either group had a re-bleed or perforated peptic ulcer during the study period. Therefore, in patients with moderately severe active peptic ulcer disease while receiving treatment with proton pump inhibitors, either approach of early conversion to clopidogrel or continuation of aspirin is safe. Future study is required to address anti-platelets strategies in bleeding peptic ulcers with endoscopic stigmata of re-bleeding.

Adverse impact of gastrointestinal bleeding in acute coronary syndrome

The efficacy of a combination of aspirin, clopidogrel and anticoagulation has been established in patients with acute coronary syndrome[15]. The American College of Cardiology / American Heart Association guidelines recommend the use of unfractionated or low molecular weight heparin in addition to aspirin and clopidogrel for the management of unstable angina or non-ST elevation myocardial infarction (class I indication).[16] Enoxaparin is preferable to unfractionated heparin in the absence of renal failure and if coronary artery bypass graft surgery is not planned within 24 hours.

The major adverse event of the combination of heparin, aspirin and clopidogrel is bleeding, particularly from the gastrointestinal tract. However, information on gastrointestinal bleeding is scarce. The incidence rate of bleeding can only be inferred from The Clopidogrel in Unstable Angina To Prevent Recurrent Events Trial[15]. This randomised controlled study primarily examined the efficacy and safety of the addition of clopidogrel to aspirin in patients with acute coronary syndrome over a mean follow-up of 9 months. Anticoagulation was used in ~ 70% of patients in both groups. Furthermore, thrombolytics was used in 1-2% of patients and glycoprotein IIb/IIIa receptor antagonist was used in 6-7% of patients in each group. Overall, the rate of early major bleeding within 30 days after randomisation was significantly higher in the combination group than the aspirin alone group (2.0 % versus 1.5 %). The most frequent site of excess major bleeding episodes was the gastrointestinal tract followed by bleeding at arterial puncture sites.

Recently, the adverse impact of bleeding in acute coronary syndrome has been recognised. In the first study[17], the association between bleeding and death or ischaemic events in 34 146 patients with acute coronary syndrome enrolled in three registries was examined. Patients with major bleeding were older, more often had diabetes or a history of stroke, had a lower blood pressure and higher serum creatinine and more often had ST-segment changes on the presenting ECG. Patients with major bleeding had a 5-fold-increase in mortality rate at 30-day (12.8% versus 2.5%; p=0.0001) and a 1.5-fold-increase in mortality rate between 30 days and 6 months (4.6% versus 2.9%; p=0.002). The severity of bleeding was associated with mortality (minor less than major less than life-threatening; *P* for trend =0.0009). In the second study[18], gastrointestinal bleeding after percutaneous coronary intervention for acute myocardial infarction in the Primary Angioplasty in Myocardial Infarction trials involving 3,130 patients was evaluated. 2.3% developed gastrointestinal bleeding, which was more likely to occur in elderly patients. Gastrointestinal bleeding was independently associated with a prolonged hospital stay (6.4 versus 12.6 days p=0.0001) and greater in-hospital mortality (2.8% versus 10%, p=0.0046) and 6-month mortality (4.6% versus. 14%, p=0.0016). This difference may be partly accounted by the premature termination of anti-platelet therapy during bleeding. In fact, premature discontinuation thienopyridine therapy 30 days after drug-eluting stent placement for acute myocardial infarction resulted in more deaths during the next 11 months (7.5% versus 0.7%, p=0.0001; adjusted hazard ratio 9.0; 95% confidence interval,1.3 to 60.6).[19] Therefore, evaluation of strategies to reduce bleeding and thereby improve clinical outcomes is urgently needed.

Prevention of upper gastrointestinal bleeding in acute coronary syndrome

What is the strategy to prevent gastrointestinal bleeding during aspirin and clopidogrel co-therapy? Unfortunately, the information is sparse. Currently, there has been no randomised controlled study published in the English literature. There are only two cohort studies.

In the first case-control study[20], upper gastrointestinal bleeding in the 30 days following PCI for stable angina and acute coronary syndromes was evaluated. The incidence of upper gastrointestinal bleeding following PCI was 1.2% (70 of 5,673 patients). The risk factors were primary PCI (odds ratio 27.80, P < 0.001), cardiac arrest (odds ratio 6.17, P = 0.003), inotropic requirement (odds ratio 5.85, P = 0.001), thienopyridine use before PCI (odds ratio 2.40, P = 0.02), and advanced age (odds ratio 1.08, P < 0.001). Endoscopy provided therapeutic intervention in 33% of patients with no serious complications during endoscopy. Prescription of proton pump inhibitors (odds ratio 0.08, P = 0.002) was accompanied with a reduced risk. The 30-day mortality for patients with upper gastrointestinal bleeding was significantly higher (11.9% versus 0.5%, P = 0.001).

In the second study[21], a cohort of 666 patients receiving a combination of aspirin, clopidogrel and enoxaparin was evaluated for upper gastrointestinal bleeding at the 7th day after stopping combination therapy. Gastrointestinal bleeding occurred in 2.7% patients. The age adjusted odds ratio (95% confidence interval) for gastrointestinal bleeding was 5.07 (1.31-16.58) for previous peptic ulcer and 21.41 (2.56-146.68) for cardiogenic shock. Co-prescription of proton pump inhibitors could reduce the risk [odds ratio 0.07 (0.01-0.27)]. A prospective randomised controlled study to evaluate the efficacy of proton pump inhibitors is warranted.

Safety of long-term proton pump inhibitors

The safety of long term administration of proton pump inhibitors in humans is not totally clear yet. In general, long term PPI therapy appears to be safe in humans. However, gastric cancer did occur in rats receiving high dose PPI therapy. Enterochromaffin-like cell carcinoids developed in 20% of rats after life long high dose omeprazole therapy[22]. Gastric carcinoma developed in 90% of rats with duodenogastric reflux after one year of omeprazole therapy[23]. Fortunately, these have not been observed in humans. Lamberts et al reported that only argyrophil cell hyperplasia secondary to PPI- induced hypergastrinaemia developed in 19% patients receiving high dose omeprazole (40 mg - 60 mg daily) for 10 years[24]. There was no gastric atrophy, intestinal metaplasia, argyrophil cell dysplasia or neoplasia. Despite this assurance, there have been reports of development of gastric fundic gland polyps and hyperplastic polyps in both adults and children receiving long-term omeprazole therapy, although their natural history and long-term clinical significance is currently unknown[15-32] .

Conclusion

In summary, in patients with no history of peptic ulcer disease or gastrointestinal bleeding, clopidogrel appears to be safer than aspirin. However, the cost-effectiveness should be analysed since 500 patients need to be treated with clopidogrel to prevent only one aspirin-induced severe gastrointestinal bleeding. In patients with dyspeptic or moderately severe bleeding peptic ulcers, both approaches of early conversion to clopidogrel or continuation of aspirin are safe if the patients are maintained by proton pump inhibitors. Future studies are required to address anti-platelet strategies in very high risk bleeding peptic ulcers, particularly requiring endoscopic haemostasis. On the other hand, long-term administration of clopidogrel alone, without proton pump inhibitor prophylaxis is unsafe in patients with history of bleeding peptic ulcer. In patients with acute coronary syndrome, the addition of clopidogrel to standard aspirin therapy reduces the rate of major adverse cardiovascular events but is associated with gastrointestinal bleeding. Bleeding is associated with adverse cardiovascular outcome. The co-prescription of proton pump inhibitors appears to reduce the risk. Long-term administration of proton pump inhibitors appears to be safe in humans. Further prospective studies for the prevention and management of gastrointestinal bleeding during aspirin and clopidogrel ± anticoagulation therapy and the role of H_2-receptor antagonist in the prevention of antiplatelet drug-induced peptic ulcer disease are warranted.

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Clinical Quiz

Clinical Quiz

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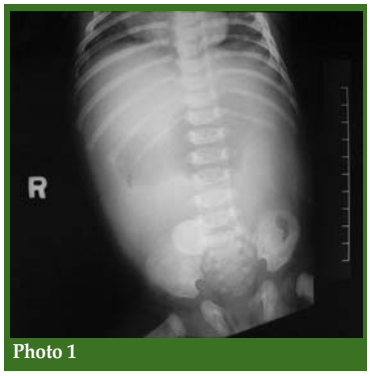

Photo 1

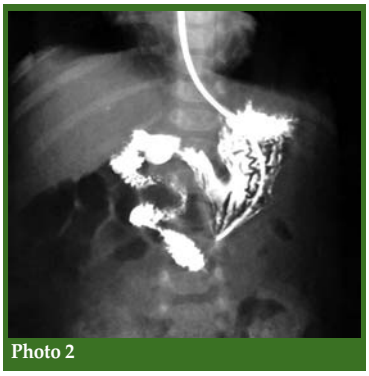
Photo 2

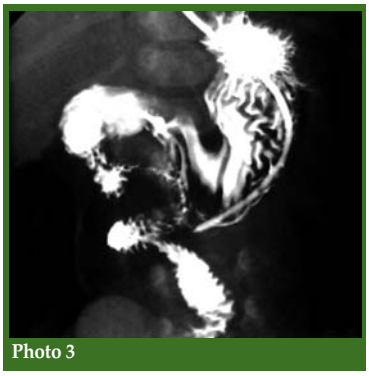
Photo 3

Clinical Information:

Two-month old baby boy presented with poor oral feeding and bilious vomiting.

Questions:

What were the radiological findings and diagnosis?

(See P.37 for answers)

Abbreviated Prescribing Information

Product Name: Zeffix™

Active Ingredient: Lamivudine

Indications: treatment of patients with chronic hepatitis B (CHB) and evidence of hepatitis B virus (HBV) replication.

Dosage & Administration: *Adults:* 100mg once daily. Children (*2-17 years old*): 3mg/kg once daily up to max. 100mg/day. Children (*<2 years old*): insufficient data to propose specific dosage recommendation in this age group. Renal impairment: serum lamivudine concentrations (AUC) are increased in patients with moderate to severe renal impairment due to decreased renal clearance. The dosage should be reduced for patients with a creatinine clearance of <50ml/min (see Table).

Table: Adjustment of Adult Dosage in Accordance with Creatinine Clearance

Creatinine clearance (ml/min)	First dose of Zeffix	Maintenance Dose Once Daily
30 to <50	100 mg	50 mg
15 to <30	100 mg	25 mg
5 to <15	35 mg	15 mg
<5	35 mg	10 mg

Contra-indication: Zeffix tablets are contraindicated in patients with known hypersensitivity to Zeffix or to any ingredients of the preparations.

Warnings and Precautions: During treatment patients should be monitored regularly during treatment by a physician experienced in the management of chronic hepatitis B. If Zeffix is discontinued or there is a loss of efficacy, some patients may experience clinical or laboratory evidence of recurrent hepatitis. Exacerbation of hepatitis has primarily been detected by serum ALT elevations, in addition to the re-emergence of HBV DNA. Most events appear to have been self-limited. Fatalities are very rare and the causal relationship to discontinuation of Zeffix treatment is unknown. If Zeffix is discontinued, patients should be periodically monitored both clinically and by assessment of serum liver function tests (ALT and bilirubin levels), for at least four months for evidence of recurrent hepatitis; patients should then be followed as clinically indicated. For patients who develop evidence of recurrent hepatitis post-treatment, there are insufficient data on the benefits of re-initiation of Zeffix treatment. In patients with moderate to severe renal impairment, serum lamivudine concentrations (AUC) is increased due to decreased renal clearance, therefore the dose should be reduced for patients with a creatinine clearance of <50 ml/min. Transplantation recipients and patients with advanced liver disease are at greater risk from active viral replication. Due to marginal liver function in these patients, hepatitis reactivation at discontinuation of Zeffix or loss of efficacy during treatment may induce severe and even fatal decompensation. It is recommended that these patients are monitored for parameters associated with hepatitis B, for liver and renal function, and for antiviral response during treatment. If treatment is discontinued for any reason, it is recommended that these patients are monitored for at least 6 months post cessation of treatment. Patients experiencing signs of hepatic insufficiency during or post-treatment should be monitored frequently, as appropriate.

HBV viral subpopulations (YMDD and HBV) with reduced susceptibility to Zeffix have been identified during extended therapy. In a minority of cases this variant can lead to recurrent hepatitis. For the treatment of patients who are coinfected with HIV and are currently receiving or are planning to receive an antiretroviral treatment regimen including lamivudine, the dose of lamivudine usually prescribed for HIV infection should be maintained. There is no information available on maternal-foetal transmission of hepatitis B virus in pregnant women receiving treatment with Zeffix. The standard recommended procedures for hepatitis B virus immunization in infants should be followed. Patients should be advised that therapy with Zeffix has not been proven to reduce the risk of transmission of hepatitis B virus to others and therefore, appropriate precautions should still be taken.

Interaction: Zeffix is predominantly eliminated by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system e.g. trimethoprim.

Administration of trimethoprim/sulphamethoxazole 160 mg/800 mg increased Zeffix exposure by about 40%. Zeffix had no effect on the pharmacokinetics of trimethoprim or sulphamethoxazole. However, unless the patient has renal impairment, no dosage adjustment of Zeffix is necessary. A modest increase in Cmax (28%) was osbserved for zidovudine when administered with Zeffix, however overall exposure (AUC) was not significantly altered. Zeffix may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. Zeffix is therefore not recommended to be used in combination with zalcitabine.

Pregnancy and Lactation: Use in pregnancy should be considered only if the benefit outweighs the risk. Although the results of animal studies are not always predictive of human response, the findings in the rabbit suggest a potential risk of early embryonic loss. Consequently, Zeffix administration is not recommended during the first three months of pregnancy. For patients who are being treatment with Zeffix and subsequently become pregnant consideration should be given to the possibility of recurrence of hepatitis on discontinuation of Zeffix. Following oral administration of lamivudine was excreted in human breast milk at similar concentrations to those found in serum (range 1 – 8 micrograms/ml).

Undesirable effects: In clinical studies of patients with chronic hepatitis B, Zeffix was well tolerated. The incidence of adverse events and laboratory abnormalities (with the exception of elevations of ALT and CPK, see below) was similar between placebo and Zeffix treated patients.

The most common adverse events reported were malaise and fatigue, respiratory tract infections, headache, abdominal discomfort and pain, nausea, vomiting and diarrhea.

Elevations of ALT; Elevation in ALT were more common post-treatment in patients treated with Zeffix than placebo. In controlled trials in patients with compensated liver disease, however, there was no appreciable difference post treatment in clinically severe ALT elevations associated with bilirubin elevations and / or signs of hepatic insufficiency, between Zeffix and placebo treated patients. The relationship of these recurrent hepatitis events to Zeffix treatment or to the previous underlying disease is uncertain.

Elevation of CPK; In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of Zeffix.

Thrombocytopenia; muscle disorders (including myalgia, cramps and rhabdomyolysis).

In patients with HIV infection, cases of pancreatitis and peripheral neuropathy (or parasthesia) have been reported, although no relationship to treatment with lamivudine (3TC™) has been clearly established. In patients with chronic hepatitis B there was no observed difference in incidence of these events between placebo and Zeffix treatment patients.

Cases of lactic acidosis, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of combination nucleoside analogue therapy in patients with HIV. There have been occasional reports of these adverse events in hepatitis B patients with decompensated liver disease, however, there is no evidence that these events were related to treatment with Zeffix.

Overdose: If overdose occurs the patient should be monitored, and standard supportive treatment applied as required.

Storage condition: Store below 30°C.

Please read the full prescribing information prior to administration.
Full prescribing information is available on request

Abbreviated Prescribing Information version 2.0 prepared in May 2007.

1. Liaw YF, Sung JJ, Chow WC et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med 2004; 351: 1521-1531.

* Disease progression is defined as a ≥ 2 points increase in Child-Pugh score, spontaneous bacterial peritonitis, renal insufficiency, bleeding varices, the development of hepatocellular carcinoma, or liver-related death.

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Hong Kong Association for the Study of Liver Diseases Annual Scientific Meeting, 23-24 November 2007

Risk Stratification for Patients with Chronic Hepatitis B

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Although the liver diseases that predispose to hepatocellular carcinoma (HCC) and liver failure are well known, not everyone with these diseases will develop these outcomes. Ideally, if it could be predicted accurately who would develop these bad outcomes, treatment strategies to prevent cirrhosis and HCC could be instituted, and screening programmes for HCC could be targeted to the appropriate population.

Among hepatitis B carriers a number of factors have been identified that confer added risk of cirrhosis and HCC. HBV DNA concentration is the best predictor of risk of HCC and cirrhosis. As HBV DNA concentration increases, risk of HCC also increases, with a threshold of risk starting to rise at an HBV DNA concentration somewhere between 104 and 105 copies/ml. This has been shown in several large scale studies. Elevated ALT is also a predictor of increased risk of cirrhosis and HCC, but not as strong a predictor as HBV DNA concentration. Other factors include advancing age, presence of fibrosis on biopsy, hepatitis B genotype C vs genotype B and genotype D vs genotype A. A risk function nomogram providing 5 and 10 year risk for HCC has been developed.

Among cirrhotic patients other factors imply increased risk of HCC or liver failure. These include ongoing viral replication, falling platelet count, and presence on biopsy of several histological markers, such as large cell change, and asymmetric regeneration.

Treatment Goals: Can Chronic Hepatitis B be Cured?

Prof. Ching-lung Lai

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The ultimate goals for the treatment of chronic hepatitis B is to prevent (or at least delay) the development of cirrhosis complications and hepatocellular carcinoma. It has been shown that prolonged suppression of viral replication with lamivudine can decrease cirrhosis complications and HCC in both patients with cirrhosis[1] and patients without cirrhosis[2]. However, especially in patients who acquire the infection early in life, i.e., most Asian, Mediterranean or African carriers, disease does progress, and complications of cirrhosis and HCC do occur, after HBeAg seroconversion, with HBV DNA levels at relatively low levels (>104 copies/mL or >2000 IU/mL) and ALT levels between 0.5-2 times the upper limit of normal (ULN)[3]. Even after clearance of hepatitis B surface antigen (HBsAg), the risk of HCC is not decreased if the patients only lose HBsAg after the age of 50[4,5].

The ideal treatment endpoint is HBeAg seroconversion together with permanent suppression of HBV DNA to below PCR detectability and normalisation of ALT levels to <0.5 ULN[6]. As to whether one can consider this as a "cure" for the disease, the fact that patients with HBsAg seroclearance can develop HCC seems to imply a negative answer. However, whether further clearance of covalently closed circular (ccc) HBV DNA in hepatocytes can be considered as a cure has yet to be investigated. That ccc DNA can be lowered with nucleos(t)ide analogue treatment has been documented[7].

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Management of HBV drug resistance

Prof. Fabien Zoulim[1,2,3]

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Despite the recent progress in antiviral therapy of chronic hepatitis B, clinical experience has shown that antiviral drug resistance is inevitable with the administration of nucleoside analog monotherapy. Several antivirals have now been approved because their antiviral efficacy is associated with an improved outcome of the liver disease during the follow-up period. The long-term persistence of the viral genome in infected cells and the high rate of spontaneous mutation is the basis for the selection of HBV mutants that are resistant to polymerase inhibitors. Selection of antiviral-resistant mutations leads to a rise in viral load and progression of liver disease. The incidence of antiviral resistance depends on the potency and genetic barrier to resistance of the antiviral drug, highlighting the importance of the choice of first line therapy. The

determination of cross-resistance profile of each drug has allowed the design of rescue therapy for patients with virologic breakthrough. Early diagnosis and treatment intervention allow the majority of patients to maintain in clinical remission despite the occurrence of drug resistance. Clinical studies are ongoing to determine the best strategy to prevent or delay antiviral drug resistance and of its impact on liver disease.

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Impact of HBV Genotypes and Mutants on HCC

Prof. Masashi Mizokami

Department of Clinical Molecular Informative Medicine, Nagoya City University, Japan

420 million people are estimated to be suffering from chronic infection of hepatitis B virus (HBV) and HBV has been a public health problem worldwide, since it was first identified in 1967. Recent studies showed eight genotypes, A-H, of HBV are distinguished by a divergence >8%. Molecular evolutionary analysis in the entire genomic sequence showed association with anthropologic and human migration. One of the most important findings in HBV genotypes is the distinct geographic distributions and their association with clinical manifestation in hosts. Genotype A and D are major genotypes in Europe and genotype A has been reported to be associated with chronic liver disease less frequently than genotype D. Nevertheless subgenotype A1(Aa), mainly in Africa, is suspected to be associated with high prevalence of hepatocellular carcinoma (HCC) with specific mutation in the precore (PC) region which is called Kozack mutation in South Africa. Genotype E is reported to be associated with progression to HBV carrier state during childhood in West Africa and genotype F is localised in the New World. There is still unclear association between HCC and specific mutations of genotype E and F. Recently identified genotype G always co-infects with genotype A and is incapable of the processing of HBeAg. The high frequency of the recombination with other genotypes is still unclear in clinical significance. In East Asia, genotype B and C are common and genotype C has higher disease-inducing capacity than genotype B with high positivity of HBeAg and mutations in basic core promoter (BCP), CP, and X region. Moreover, genotype B is classified into 2 subgenotypes, B1(Bj) and B2(Ba). Ba is located in Asian countries except Japan and recombined with genotype C in the core and BCP region. Interestingly, determination of cross-resistance profile of each drug has allowed the design of rescue therapy for patients with virologic breakthrough. Early diagnosis and treatment intervention allow the majority of patients to be maintained in clinical remission despite the occurrence of drug resistance. Clinical studies are ongoing to determine the best strategy to prevent or delay antiviral drug resistance and its impact on liver disease. Ba is strongly associated with HCC among the young generation. These data indicated that clinical differences among HBV genotypes would be attributable to the infected hosts and genome structure of HBV genotypes. To investigate these differences, we developed HBV transfection system using 1.24-fold HBV genome constructs belonging to HBV genotypes, Aa, A2(Ae), Bj, Ba, C and D and Huh7 cells for in vitro test, and severe combined immunodeficient mice transgenic for urokinase-type plasminogen activator transfected with human hepatocyte (chimeric mice) for in vivo test. HBV DNA levels in cell lysates of Huh 7 cells were the highest for C, followed by Bj, Ba, D and Ae ($P < 0.01$) and the lowest by Aa ($P < 0.01$), whereas in culture media, they were the highest for Bj, distantly followed by Ba, C and D ($P < 0.01$), and further by Ae and Aa ($P < 0.01$). HBV Core protein was about 3-fold higher for D than Ae and Aa. Cellular retention in Huh 7 cells was higher for C and Ba than other genotypes. HBsAg was most abundant for Ae followed by Aa, Ba, Bj, and C and remotely by D, which was consistent with mRNA levels. The HBV DNA levels expressed in the chimeric mice were higher for C than Ae by 2 logs at 4 to 7 weeks postinoculation. In conclusion, virologic differences in HBV genotypes were demonstrated both in tissue culture and the chimeric mice. These differences can explain the different clinical manifestations of HBV infections with distinct genotypes in the host.

Local Ablative Treatment of HCC

Prof. Ronnie Poon

Department of Surgery, The University of Hong Kong, Hong Kong

Local ablative treatment is a potentially curative treatment for hepatocellular carcinoma (HCC) not amenable to resection or liver transplantation. Percutaneous ethanol injection (PEI) used to be the main modality of local ablative therapy. In recent years, various thermal ablative therapies such as radiofrequency ablation (RFA), microwave and high intensity focused ultrasound (HIFU) have been developed. RFA is currently the most widely used modality of ablative therapy for HCC and has been proven to achieve more complete ablation and better long-term survival compared with PEI in randomised controlled trials. It employs thermal energy of vibration of ions in cells induced by radiofrequency wave to achieve protein coagulation and cell death. It has the merits of a minimally invasive therapy that can achieve effective local tumour ablation and preservation of normal liver parenchyma. Studies have demonstrated a complete ablation rate of above 90% for liver tumours less than 5 cm in diameter, and a treatment mortality rate of less than 1%. However, the safety of RFA depends on careful case selection and appropriate choice of approaches, which can be percutaneous, laparoscopic, thoracoscopic or open. While RFA is technically simpler compared with surgical resection of liver tumour, there is a learning curve that has to be overcome before RFA can be offered with satisfactory outcome. RFA is currently used mainly for unresectable HCC. It has offered a potentially curative treatment for patients with small HCC but poor liver function due to underlying cirrhosis, who otherwise did not have effective treatment in the past except for liver transplantation. There is some preliminary evidence that RFA may achieve survival results comparable to that of liver resection for small HCCs, although the evidence is not strong enough to recommend RFA as a replacement of resection. A high local recurrence rate is a problem of RFA that requires further research to resolve. Microwave and HIFU are two emerging modalities that may offer some advantages over RFA. It is foreseeable that the role of local ablative treatment of HCC will continue to expand in the near future.

CERTIFICATE COURSE FOR MIDWIVES, NURSES AND OTHER ALLIED HEALTH WORKERS

Update on Obstetrics
產科新里程

Jointly organized by:

The Federation of Medical Societies of Hong Kong
香港醫學組織聯會

The Obstetrical and Gynaecological Society of Hong Kong
香港婦產科學會

Objective: This course is aimed for midwives, nurses, general practitioners or other allied health workers who are interested to learn about the recent advances in the field of obstetrics. There are many changes in the management of pregnant women right from the antenatal period, including invasive and non-invasive prenatal diagnostic techniques, management of the normal, abnormal and high risk pregnancies. Advances in the intrapartum and postpartum management will also be discussed. The concept and delivery of midwifery care have undergone tremendous changes in the recent decade and will be further explored.

Date	Speaker	Topic
3 Apr 2008	梁德楊醫生 Dr. Leung Tak Yeung	唐氏綜合症之篩查 Down Syndrome Screening 胎位不正之處理 Malpresentation and Management
10 Apr 2008	林兆強醫生 Dr. Lam Siu Keung	產前產後出血之處理 Antepartum, Postpartum Haemorrhage 產科法律訴訟 Medicolegal Issues
24 Apr 2008	梁國賢醫生 Dr. Leung Kwok Yin	胎兒監察新知/多胞胎之處理 Update on Fetal Assessment/Multiple Pregnancy Management
8 May 2008	李德誠醫生 Dr. Lee Tak Shing, Dominic	產前產後之情緒變化 Mood Changes in Antenatal and Postnatal Period
15 May 2008	歐陽錦全醫生 Dr. Au Yeung Kam Chuen	產科重病新知識 Serious Disorder in Antenatal Period and Management
22 May 2008	黎哲瑩專科護士 Miss Lai Chit Ying	助產士在現代產科的角色 Midwifes' Role in Modern Obstetric Care

Date : April 3, 10, 24 & May 8, 15, 22, 2008
Time : 7:00 p.m. - 8:30 p.m.
Venue : Lecture Hall, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, HK
Course Fee : HK$750 (6 Sessions)
Language : Cantonese supplemented with English
Certificate : Awarded to participants with a minimum attendance of 70%
Enquiry : The Secretariat of the Federation of Medical Societies of Hong Kong
Tel. : 2527 8898 Fax : 2865 0345 Email : info@fmshk.org

CME/CPD accreditation applied; OGSHK CNE/PEM point pending
To download the application form, please visit our website: http://www.fmshk.org

Medical Diary of March

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
						1
★ Kidney Disease Awareness Day ★ Glaucoma Public Awareness Day 2	★ When Should We Take an Infected Kidney Out? 3	★ FMSHK Officers' Meeting 4	5	★ HKMA Council Meeting 6	7	★ Refresher Course for Health Care Providers 2007/2008 (VII) - Counselling in Primary Care 8
★ Football Day ★ HKMA Structured CME Programme at Queen Elizabeth Hospital Year 07/08 (XII) - Clinical Oncology and Cardiothoracic Surgery 9	10	★ HKMA Newsletter Editorial Meeting ★ Wound Management in Disasters (Code No. SE-WMD-0108) 11	★ Hong Kong Neurosurgical Society Monthly Academic Meeting - Radiosurgery : Past, Present & Future ★ Joint Professional Golf Tournament 2008 12	★ HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2008 (III) 13	★ Advanced Trauma Life Support (ATLS) Provider Course 14	★ Advanced Trauma Life Support (ATLS) Provider Course 15
★ Advanced Trauma Life Support (ATLS) Provider Course 16	17	★ 8 Lessons in Practical Psychiatry for General Practitioners: A Certificate Course ★ FMSHK Executive Committee Meeting 18	19	20	21	22
23	24	25	★ Interpretation of Arterial Blood Gases and Essential Electrolytes Imbalance 26	★ 8 Lessons in Practical Psychiatry for General Practitioners: A Certificate Course 27	28	29
★ HKMA Structured CME Programme at Kwong Wah Hospital Year 07/08 (XII) - Rehabilitation & Palliative Care 30	31					

Medical Diary of March

Date / Time	Function	Enquiry / Remarks
2 1:00 pm **SUN**	**Kidney Disease Awareness Day** Organised by: The Hong Kong Medical Association # Hospital Authority Building, 147B Argyle Street, Kowloon **Glaucoma Public Awareness Day** Organised by: The Hong Kong Ophthalmological Society & College of Ophthalmologists of Hong Kong # Grand Century Place, Mongkok, Kowloon	Miss Gloria CHEUNG Tel: 2527 8285 Dr. Dexter LEUNG Email: dexleung@gmail.com
3 7:30 pm - 8:30 pm **MON**	**When Should We Take an Infected Kidney Out?** Organised by: Hong Kong Urological Association Speaker: Dr. LAM Kin Man # Seminar Room, G/F., Block A, Queen Elizabeth Hospital, Kowloon, Hong Kong	Dr. CHAN Kwok Keung, Sammy/Ms Siddy MA Tel: 2958 6006 Fax: 2958 6076 1 CME Point
4 8:00 pm - 10:00 pm **TUE**	**FMSHK Officers' Meeting** Organised by: The Federation of Medical Societies of Hong Kong # Gallop, 2/F., Hong Kong Jockey Club Club House, Shan Kwong Road, Happy Valley, Hong Kong	Secretariat Tel: 2527 8898 Fax: 2865 0345
6 8:00 pm **THU**	**HKMA Council Meeting** Organised by: The Hong Kong Medical Association Chairman: Dr. K CHOI # HKMA Head Office, 5/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Christine WONG Tel: 2527 8285
8 2:30 pm **SAT**	**Refresher Course for Health Care Providers 2007/2008 (VII) - Counselling in Primary Care** Organised by: The Hong Kong Medical Association & Our Lady of Maryknoll Hospital Speaker: Dr. Anthony HO # Training Room II, 1/F, OPD Block, Our Lady of Maryknoll Hospital, 118 Shatin Pass Road, Wong Tai Sin, Kowloon, Hong Kong	Ms. Clara TSANG Tel: 2354 2440 2 CME Points
9 12:00 pm **SUN** 2:00 pm	**Football Day** Organised by: The Hong Kong Medical Association Chairman: Dr. K CHAN & Dr. T CHAN # CUHK Football Ground **HKMA Structured CME Programme at Queen Elizabeth Hospital Year 07/08 (XII) - Clinical Oncology and Cardiothoracic Surgery** Organised by: The Hong Kong Medical Association & Queen Elizabeth Hospital Speaker: Dr. SO Ping Fai, Peter & Dr. LO Cheuk Kin # Lecture Theatre, G/F, Block M, Queen Elizabeth Hospital, Kowloon	Ms. Dora HO Tel: 2527 8285 Miss Viviane LAM Tel: 2527 8452 (Registration Fee is required) 3 CME Points
11 8:00 pm **TUE** 7:00 pm - 8:30 pm	**HKMA Newsletter Editorial Meeting** Organised by: The Hong Kong Medical Association Chairman: Dr. H.H. TSE # HKMA Head Office, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong **Wound Management in Disasters (Code No. SE-WMD-0108)** Organised by: College of Nursing, Hong Kong Speaker: Ms. YIU Miu Fan, Esther	Ms. Tammy TAM Tel: 2527 8941 Secretariat Tel: 2572 9255 Fax: 2838 6280 1.5 CNE Point
12 7:30 am **WED** 12:00 pm	**Hong Kong Neurosurgical Society Monthly Academic Meeting - Radiosurgery : Past, Present & Future** Organised by: Hong Kong Neurosurgical Society Chairman: Dr. K.Y. YAM Speaker: Dr. Rebecca NG # Seminar Room, G/F, Block A, Queen Elizabeth Hospital, Kowloon **Joint Professional Golf Tournament 2008** Organised by: The Hong Kong Medical Association Chairman: Dr. L HOU # Jockey Club Kau Sai Chau Public Golf Course	Dr. Y.C. PO Tel: 2990 3788 Fax: 2990 3789 2 CME Points (College of Surgeons of Hong Kong) Ms. Dora HO Tel: 2527 8285
13 2:00 pm **THU**	**HKMA Structured CME Programme with Hong Kong Sanatorium & Hospital Year 2008 (III)** Organised by: The Hong Kong Medical Association & Hong Kong Sanatorium & Hospital Speaker: Dr. Arthur C.K. CHENG # HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	Miss Viviane LAM Tel: 2527 8452 (Registration Fee is required) 1 CME Point
14 (15,16) **FRI**	**Advanced Trauma Life Support (ATLS) Provider Course** Organised by: Skills Development Centre, Department of Surgery, Li Ka Shing Faculty of Medicine, The University of Hong Kong & the American College of Surgeons, Hong Kong Chapter # Skills Development Centre, Department of Surgery, Li Ka Shing Faculty of Medicine, University of Hong Kong Medical Center, Queen Mary Hospital, Pokfulam, Hong Kong	Program Manager Tel: (852) 2855 4885 / 2855 4886 Fax: (852) 2819 3416 E-mail: qmhsdc@hkucc.hku.hk
18 2:00 pm **TUE** 8:00 pm - 10:00 pm	**8 Lessons in Practical Psychiatry for General Practitioners: A Certificate Course** Organised by: The Hong Kong Medical Association Speaker: Prof. TANG Siu Wa # Harbour Plaza Resort City, 18 Tin Yan Road, Tin Shui Wai, N.T. **FMSHK Executive Committee Meeting** Organised by: The Federation of Medical Societies of Hong Kong # Council Chambers, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Miss Gloria CHEUNG Tel: 2527 8285 1 CME Point Secretariat Tel: 2527 8898 Fax: 2865 0345
26 6:00 pm - 8:00 pm (2 April 08) **WED**	**Interpretation of Arterial Blood Gases and Essential Electrolytes Imbalance** Organised by: Hong Kong Society for Nursing Education Speaker: Ms. HO Kam Tak, Camille # Lecture Theatre, G08, School of General Nursing, Queen Elizabeth Hospital, Kowloon, Hong Kong	Mr. Jacky LAM Tel: 9524 6160 4 CNE Points
27 **THU**	**8 Lessons in Practical Psychiatry for General Practitioners: A Certificate Course** Organised by: The Hong Kong Medical Association Speaker: Dr. CHOI Kin, Dr. CHENG Chi Man & Dr. WONG Tai Wai # Harbour Plaza Resort City, 18 Tin Yan Road, Tin Shui Wai, N.T.	Miss Gloria CHEUNG Tel: 2527 8285 1 CME Point
30 2:00 pm **SUN**	**HKMA Structured CME Programme at Kwong Wah Hospital Year 07/08 (XII) - Rehabilitation & Palliative Care** Organised by: The Hong Kong Medical Association & Kwong Wah Hospital Speaker: Dr. WONG Kam Cheung & Dr. TSANG Mei Ling # Lecture Theatre, G/F, Block M, Queen Elizabeth Hospital, Kowloon	Miss Viviane LAM Tel: 2527 8452 (Registration Fee is required) 3 CME Points

Meetings

2-4/5/2008	**16th Annual Scientific Congress of Hong Kong College of Cardiology** Organised by: Hong Kong College of Cardiology Chairman: Dr. CHIANG Chung Seung # Sheraton Hong Kong Hotel & Towers, 20 Nathan Road, Tsimshatsui, Kowloon Enquiry: Ms. Dora HO Tel: 2527 8285 Fax: 2865 0943 Email: dorahkma@hkma.org Website: http://www.hkcchk.com/scientificcongress.php
17-18/5/2008	**9th Regional Osteoporosis Conference** Organised by: Osteoporosis Society of Hong Kong & Hong Kong College of Radiologists Speaker: International & Regional Experts # Hong Kong Convention & Exhibition Centre Enquiry: Ms. Lenora YUNG Tel: 2871 8787 Fax: 2871 8898 CME Accreditation for HKCP, HKCFP, HKCR, HKCOS, HKCOG, HKCCM, HKDU, HKMA
24-25/5/2008	**Annual Scientific Meeting "Family Physicians and Our Community"** Organised by: Hong Kong College of Family Physicians Chairman: Dr. Winnie W.Y. CHAN # HKAM Jockey Club Building Enquiry: Ms. Erica SO Tel: 2528 6618 Fax: 2866 0618
11-12/7/2008	**Hong Kong Surgical Forum, Summer 2008** Organised by: Department of Surgery, Li Ka Shing Faculty of Medicine, University of Hong Kong Medical Centre; Queen Mary Hospital & Hong Kong Chapter of the American College of Surgeons # Underground Lecture Theatre, New Clinical Building, Queen Mary Hospital, Pokfulam, Hong Kong Enquiry: Forum Secretary Tel: 2855 4885 Fax: 2819 3416 Email: hksf@hkucc.hku.hk Website: http://www.hku.hk/surgery
20-22/2/2009	**CardioRhythm 2009** Organised by: Hong Kong College of Cardiology & Chinese Society of Pacing and Electrophysiology Co-Chairman: Prof. LAU Chu Pak Enquiry: Secretariat Tel: 2899 2035 Fax: 2899 2045 Email: info@cardiorhythm.com Website: http://www.cardiorhythm.com

Courses

2,9,16,23,30/5/2008 6,13,20,27/6/2008 6:30 pm to 9:30 pm	**Certificate Course in Ward Management - Module III: "Managing risk at workplace" (Code No. TC-WM-0107III)** Organised by: College of Nursing, Hong Kong Enquiry: Secretariat Tel: 2572 9255 Fax: 2838 6280
16,17/5/2008	**ISCD Bone Densitometry Course** Organised by: Osteoporosis Society of Hong Kong Chairman: Prof. Annie KUNG Speaker: International & Local Experts # Hong Kong Convention and Exhibition Centre, Wanchai, Hong Kong Enquiry: Ms. Lenora YUNG Tel: 2871 8787 Fax: 2871 8898 CME Accreditation for HKCP, HKCFP, HKCR, HKCOS, HKCOG, HKCCM, HKDU, HKMA

Upcoming Certificate Courses of the Federation of Medical Societies of Hong Kong

Date	Course No	Course Name	Co-organiser	Target Participants
3 Apr - 22 May 08	C128	Update on Obstetrics	The Obstetrical and Gynaecological Society of Hong Kong	Midwives, Nurses and other Allied Health Workers
10 Jun - 8 Jul 2008	C129	Certificate Course on Drug Dispensing in Office Clinics		Medical and Health Care Professional

Answer to Clinical Quiz

Answer - Malrotation

The abdominal radiograph shows that the stomach and the proximal duodenum are distended with air. The bowels are otherwise devoid of bowel gas. Features are suggestive of duodenal obstruction.

Upper GI contrast study is thus proceeded to find out the possible causes of obstruction. It shows that the duodenojejunal junction is abnormally on the right side of the vertebral column and below the level of the duodenal bulb. Twisting or cockscrew appearance suggesting Ladd's band is seen at the distal duodenum and proximal jejunum which are located on the right side of the abdomen. Findings are compatible with malrotation.

Malrotation associated with midgut volvulus is a surgical emergency in infants which can lead to bowel obstruction, ischaemia and necrosis. The baby boy had an urgent operation (Ladd's procedure) and the radiological findings weve confirmed.

Dr. Ka-kin Wong
MBBS, FRCR
Queen Mary Hospital

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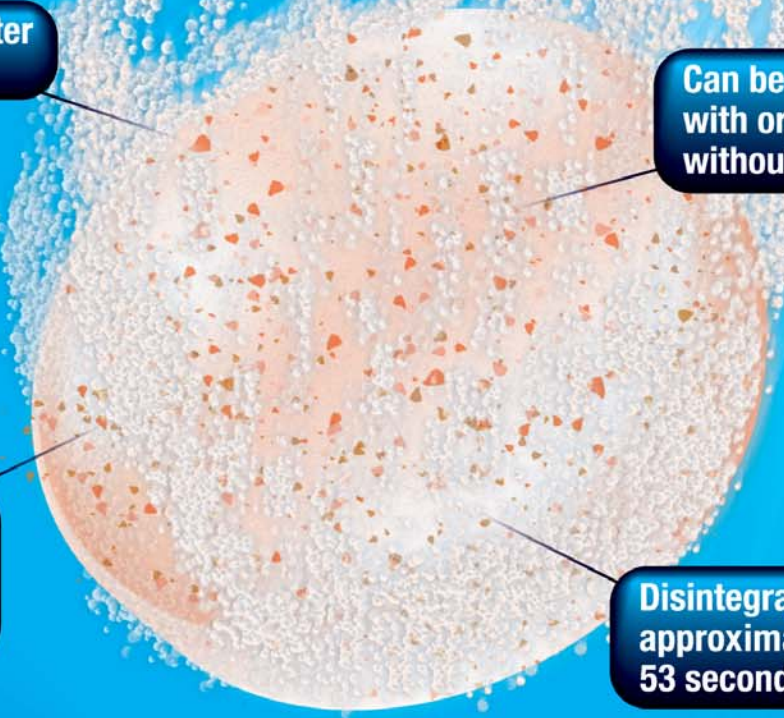

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References:

1. Baldi F et al: Lansoprazole Fast Disintegrating Tablet: A new formulation for an established PPI. Digestion 2003; 67:1-5 **2.** Takepron® package insert, Takeda Chemical Industries (Taiwan) Ltd. – Hong Kong Branch **3.** Taubel JJ et al. A comparison of simplified lansoprazole suspension administered nasogastrically and pantoprazole administered intravenously: effects on 24-h intragastric pH. Aliment Pharmacol Ther 2001; 15: 1807-1817 **4.** PREVACID (lansoprazole) complete prescribing information. **5.** Earnest DL, Dorsh E, Jones J, et al. Am J Gastroeterol 1998;93:239-243 **6.** Robinson M, Sahba B, Avner D, et al. Aliment Pharmacol Ther 1995;9:25-31

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